

American Journal of Obstetrics and Gynecology

VOL. 59

FEBRUARY, 1950

No. 2

Original Communications

RADICAL PANHYSTERECTOMY, PELVIC LYMPH NODE EXCISION, TOTAL VAGINECTOMY, AND TOTAL CYSTECTOMY

**A One-Stage Operation for Carcinoma of the Female Genitals Invading
the Bladder.**

(Report of Twenty-One Cases)

ALEXANDER BRUNSCHWIG, M.D., MICHAEL J. JORDAN, M.D., AND
VIRGINIA K. PIERCE, M.D., NEW YORK, N. Y.

(From the Memorial Hospital Center for the Treatment of Cancer and Allied Diseases)

IN A previous report by one of us (A. B.), a procedure was described for excision of all pelvic viscera and bilateral implantation of the ureters into the sigmoid colon with end abdominal colostomy.¹ The indication for this operation is involvement of bladder and colon by a malignant neoplasm primary in the uterus. The operation, obviously a very radical one, necessitates a permanent wet colostomy since urine, as well as feces, is discharged from the colostomy.

There are patients in whom carcinoma of the cervix, vagina, or vulva has recurred or progressed to involve the bladder and in whom the rectum is not involved. A procedure for excision of the entire vagina, bladder, uterus, and pelvic lymph nodes with bilateral ureteral implantation into the colon was carried out in an attempt to encompass the neoplasm and its extensions and to spare the pelvic colon. This operation may be briefly described as follows (Figs. 1 and 2):

General anesthesia was employed in all instances.

1. Low mid-line incision extends several centimeters above the umbilicus.
2. When the absence of metastases beyond the pelvis has been confirmed, the patient is put into Trendelenburg position and bowels retracted upward.
3. The peritoneum over the upper right common iliac vessels is incised and nodes and areolar tissue about these vessels are stripped downward. The right ovarian ligament and vessels are divided.
4. The right hypogastric artery is isolated near its origin, ligated and divided. The hypogastric vein is also divided between ligatures or in some instances may be spared.

NOTE: The Editors accept no responsibility for views and statements of authors as published in their "Original Communications."

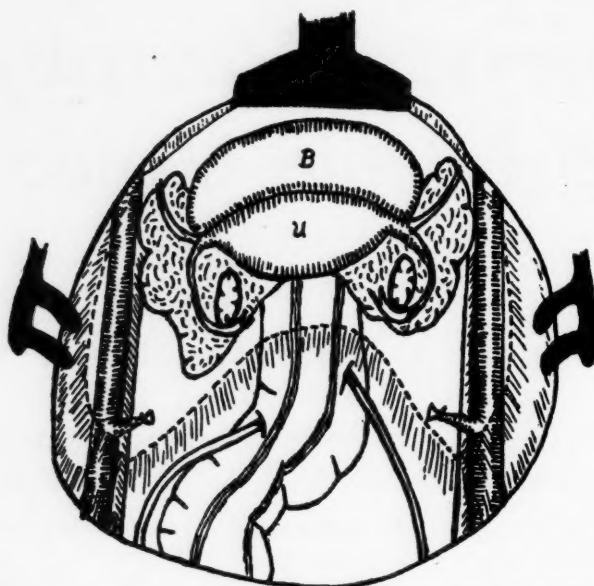


Fig. 1.—Schematic representation of operation for excision of uterus, adnexa, pelvic lymph nodes, and bladder, with bilateral transplantation of ureters into pelvic colon as seen through abdominal incision at the close of abdominal phase of procedure. B, U, bladder and uterus, respectively, not having been separated, are mobilized except for their inferior attachments, together with adnexa and broad ligament with peritoneum and nodes from lateral pelvic walls. The hypogastric arteries have both been tied and transected.

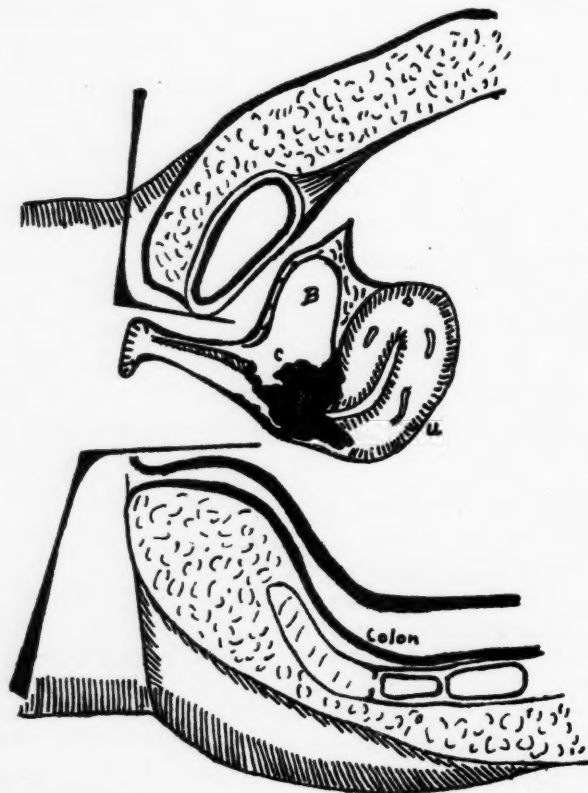


Fig. 2.—Schematic representation of perineal phase of operation. The vaginal orifice with urethra has been closed over by a continuous suture and detached from pelvic floor. A retractor depresses anal colon. The bladder, B, and uterus, U, are being removed en masse. C represents carcinoma of cervix invading posterior portion of bladder.

5. The peritoneum along the upper border of the right external iliac artery is incised along the whole extent of the vessel. This permits entrance into the right lateral retroperitoneal spaces. By means of instrument and digital dissection the areolar tissues and lymph nodes of the lateral extraperitoneal space are pushed mesially. The obturator nerve is freed and left uninjured. The right ureter is divided as low as possible but well above any gross evidence of neoplasm.

6. The same procedure as described above (Steps 3, 4, and 5) is carried out on the left side.

7. The bladder is mobilized backward from the symphysis and pubic rami on each side. The round ligaments are divided near the anterior abdominal wall.

8. The rectal colon is separated from the posterior vaginal wall almost to the perineal floor. The uterosacral ligaments are divided and transected vessels are ligated.

9. The ureters are implanted into the pelvic colon at convenient levels.

10. The abdominal incision is closed with sump drain in the lower angle and the patient placed in lithotomy position.

11. The introitus is closed by continuous suture. The clitoris and labia minora are spared.

12. Incision with the knife is made transversely below the clitoris and carried downward on each side mesial to the labia minora to meet at a point just anterior to the anus. Dissection is carried upward to free the vaginal attachments to the pelvic floor. When this is completed the entire vagina and uterus with bladder adherent are removed downward through the opening in the anterior portion of the pelvic floor.

13. The deep fatty areolar tissue is approximated with interrupted catgut sutures. The skin is closed in similar fashion. A hard rubber tube is placed in the upper angle of the wound. If oozing is appreciable a gauze pack is inserted to be removed in twenty-four hours.

The above-described operation was performed in twenty-one patients. In one instance only was the procedure done in two stages, the first stage consisting of bilateral ureterosigmoidal anastomoses. (This patient succumbed twelve hours later of massive uncontrolled hemorrhage after the second stage. Necropsy revealed no large open vessels. It appeared that the blood would not clot.²)

In six patients summarized later the results are judged to be satisfactory. Four are living and at this writing show no evidence of recurrent disease. One patient died one year and three weeks after operation. She had been examined by one of us (A. B.) three weeks before death and the pelvis was negative for evidence of local recurrence. She collapsed suddenly while at work in her home city and died three days later; necropsy was not obtained.

This group of patients represents 28.5 per cent of the series herein reported and is regarded by the writers as a salvaged group in view of the advanced stage of the disease encountered.

Case Reports (Results as of Dec. 1, 1949)

CASE 1.—Lath., 60 years old. Large ulcerating squamous-cell carcinoma of cervix extending forward into bladder. Pyometra. Vesicovaginal fistula. No previous treatment.

Operation: Nov. 11, 1947. Convalescence satisfactory. Returned to full-time office work. Nov. 10, 1948, no evidence of recurrence. Became suddenly ill while at work and died three days later in another city, Dec. 5, 1948. (Necropsy not obtained.) Cause of death: coronary occlusion? cerebral metastases? Survived 1 year, 3 weeks.

CASE 2.—G. T., 34 years old. Supracervical hysterectomy two years previously, bloody vaginal discharge persisted. Biopsy of cervical lesion revealed squamous-cell carcinoma. Vaginal cone x-ray therapy completed Sept. 15, 1947, 4,500 r. to each of three ports. Disease persisted and invaded posterior bladder wall.

Operation: Dec. 11, 1947. Convalescence essentially uneventful. *Living and well two years after operation.* No evidence of recurrence (Fig. 3).

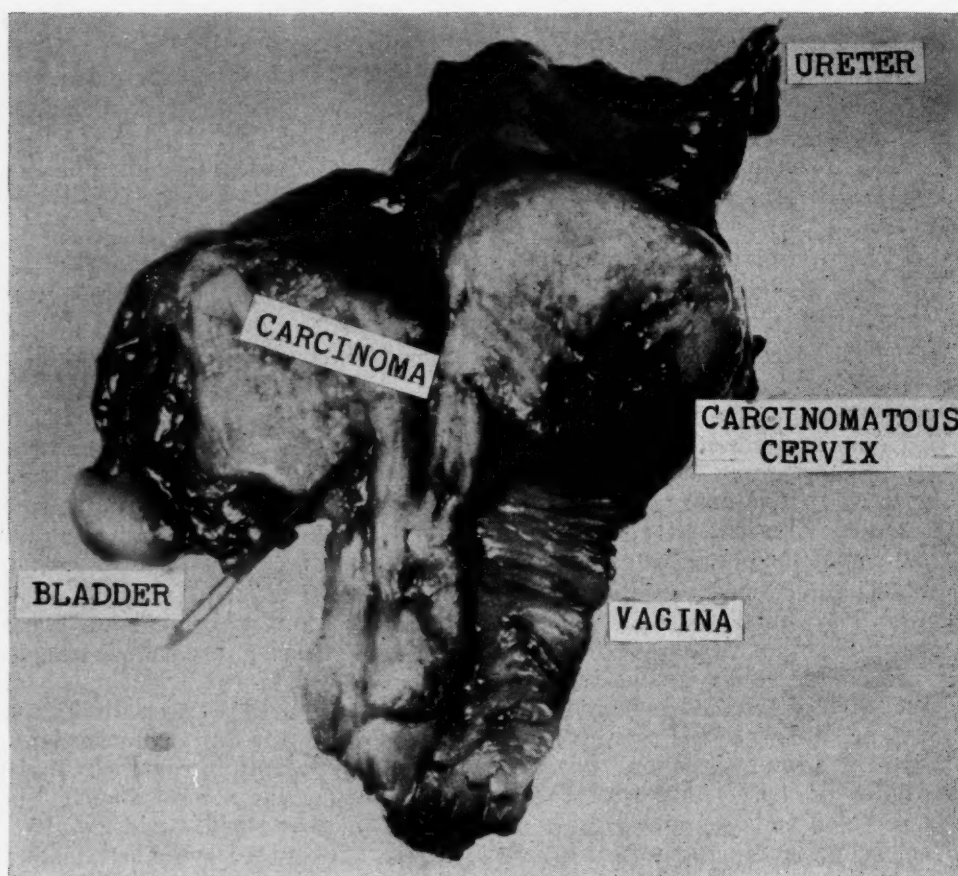


Fig. 3.—Photograph of bisected surgical specimen removed from patient in Case 2, showing carcinoma of cervical stump, vagina, bladder, etc.

CASE 3.—Kl., 44 years old. Squamous-cell carcinoma replacing entire cervix with invasion of base of bladder on right side and infiltration into parametrium on both sides.

Operation: Aug. 19, 1948. (Operation by Dr. M. J. Jordan.) *Living and well without evidence of recurrence one year and six months after operation.*

CASE 4.—Apar., 59 years old. Vaginal bleeding of three months' duration. Examination revealed ulcerating lesion invading entire anterior vaginal wall and cervix. Biopsy: Squamous-cell carcinoma. X-ray therapy by means of vaginal cones; total dose 3,750 r. completed Aug. 8, 1948. Regression of lesion in vagina but extension into parametrium on both sides and forward into bladder.

Operation: Sept. 14, 1948. *Living and well without evidence of recurrence one year, three months after operation.*

CASE 5.—Ber., 58 years old. In February, 1948, the diagnosis of squamous-cell carcinoma of the cervix was made and 6,375 mg. hr. radium applied followed by "pelvic cycles" of x-

radiation. Persistent disease was confirmed by biopsy one month prior to last admission. At laparotomy invasion of the posterior superior portion of the bladder wall was noted.

Operation: Sept. 10, 1948. Lived nine months and died of recurrences.

CASE 6.—Zasl., 61 years old. Squamous-cell carcinoma of vulva 6 by 5 cm. on left side and extending across mid-line to upper right portion of labia minora, surrounding urethra and extending upward for short distance on anterior vaginal wall.

Operation: March 11, 1948. Second operation, radical bilateral inguinal lymph adenectomy for metastatic squamous-cell carcinoma, Sept. 28, 1948. Nodes on left side only found involved. Living and well without evidence of recurrent or metastatic disease one year and nine months after initial operation (Fig. 4).

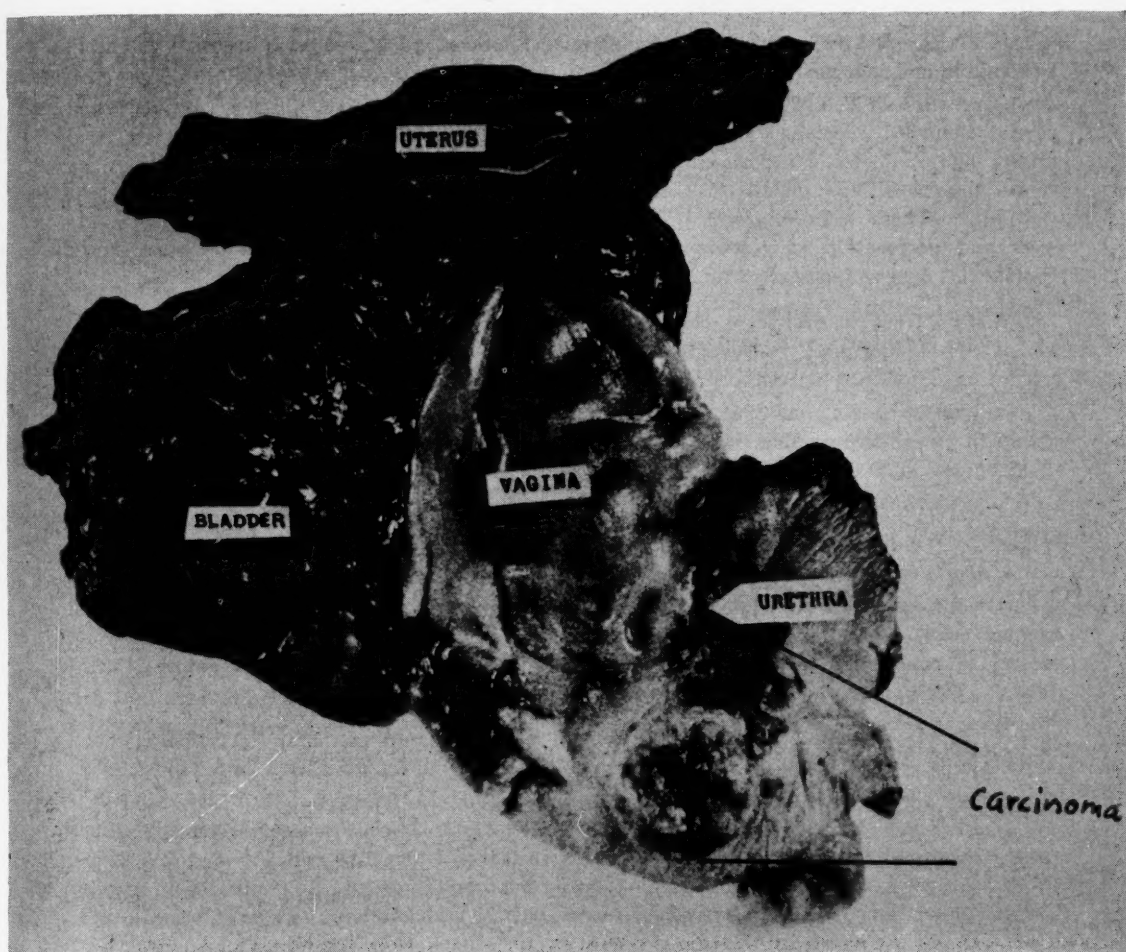


Fig. 4.—Photograph of bisected surgical specimen removed from patient in Case 6. Shows carcinoma of vulva invading base of bladder in periureteral region.

In the following group of patients there was survival for more than four weeks following operation but these are patients who at this writing have died from one cause or another.

CASE 7.—Far., 36 years old. Carcinoma of cervix previously treated by radiation therapy with failure to control disease and extension onto bladder.

Operation: Nov. 20, 1947. On the ninth day, a fecal fistula developed through perineal wound. Patient was discharged from hospital Dec. 23, 1947. Followed in Out Patient Department and readmitted because of severe pelvic pain radiating down legs Jan. 21, 1948. Discharged for terminal care Feb. 2, 1948; died Feb. 18, 1948. Survived operation 3 months. Death presumably due to widespread metastases.

CASE 8.—Broph., 57 years old. Squamous-cell carcinoma of cervix with extension far into right parametrium and onto right ureter producing marked constriction and hydronephrosis.

Operation: Sept. 21, 1948. Discharged Oct. 16, 1948. Condition fairly satisfactory at home for brief period; left thrombophlebitis. Readmitted to other hospital, bouts of sharp rises in temperature, abdominal distention, adynamic ileus, and elevated blood urea nitrogen (over 60). Died Nov. 28, 1948. Necropsy revealed bilateral pyelonephritis. No residual neoplasm. Survived 2 months following operation.

CASE 9.—Del., 58 years old. Anaplastic carcinoma of uterus with massive extension into vagina and involvement of bladder.

Operation: Feb. 2, 1948. Postoperatively there was a pelvic abscess (drained) and partial wound disruption. These complications were apparently being overcome when fecal fistula developed through perineal wound. Death occurred March 26, 1948. Necropsy revealed peritoneal and hepatic metastases not present at operation, also metastases in the vertebrae. There were bilateral pyelonephritis with multiple cortical abscesses, pelvic abscess and perforation of colon proximal to colostomy (not at ureterocolic implantation). Patient had survived operation for 7 weeks and 3 days.

CASE 10.—Gos., 61 years old. Squamous-cell carcinoma of cervix with extensive invasion of bladder and vesicovaginal fistula, extension into left parametrium; previously treated unsuccessfully by radiation.

Operation: Nov. 4, 1948. Immediate convalescence satisfactory but then developed fistula of upper ileum; this was repaired. Died Dec. 4, 1948; necropsy not obtained. Survived operation 30 days.

CASE 11.—Barba, 34 years old. Squamous-cell carcinoma of cervical stump previously treated by irradiation but uncontrolled. Extensive involvement of bladder with vesicovaginal fistula and invasion of lower anterior wall of anal canal.

Operation: Oct. 18, 1947. Convalescence satisfactory. Because lower anterior wall of anal colon was excised there was marked weakness of anal sphincter and practically no control of excreta. General condition seemed fairly satisfactory for a few months. Died July 7, 1948, of widespread metastases. Survived operation 8½ months.

CASE 12.—Herrel, 37 years old. Received x-ray and radium therapy for squamous-cell carcinoma of cervix 1946. Neoplasm recurred in situ and extended well into parametrium and base of bladder.

Operation: Feb. 7, 1948. (Operation by Dr. M. J. Jordan.) Convalescence uneventful. Discharged on twentieth day. Returned to fairly active life and traveled to Europe. In Sweden received further irradiation therapy because of obscure abdominal pain. After therapy was started, patient developed severe nausea and vomiting; was not hospitalized; died; autopsy not obtained. Survived operation for a little more than 6 months.

CASE 13.—Stad., 58 years old. Received radium treatment five months previously for squamous-cell carcinoma of cervix; progression of disease to invasion of parametrium on both sides and bladder.

Operation: Feb. 3, 1948. At operation marked hydroureter and extensive invasion of parametrial and obturator nodes as well as invasion of bladder. On seventeenth postoperative day a fecal and urinary fistula developed through the perineal wound. Patient discharged on twenty-third day. Died, presumably of advancing disease and septicemia March 7, 1948, having survived operation 4 weeks and 4 days.

CASE 14.—Amo., 49 years old. Purulent and hemorrhagic vaginal discharge five months. Large ulcerous crater replacing cervix.

Operation: Nov. 1, 1947. (Operation by Dr. Mason Morfit.) Discharged on sixteenth postoperative day. Seen in Out Patient Department on several occasions up to Jan. 1, 1948. Clinical examination showed no evidence of recurrence. Lost contact until word received that she died in another hospital Feb. 10, 1948. Cause? Survived operation 3 months and 10 days.

CASE 15.—W. K., 45 years old. Carcinoma of cervix discovered one year previously and treated by radium and x-rays. Well until October, 1948, when biopsies revealed recurrence and extension into base of bladder and into parametrium to pelvic walls. Further x-ray therapy was started but was poorly tolerated.

Operation: Jan. 12, 1949. (Operation by Dr. M. J. Jordan.) Patient was discharged from hospital on the eighteenth postoperative day. General condition was satisfactory. Returned to hospital four weeks after operation to be transfused because of severe anemia. Died suddenly on Feb. 12, 1949. Necropsy revealed no apparent cause of death, no evidence of tumor. Survived 4 weeks and 4 days after operation.

Surgical mortality is defined arbitrarily in this report as death within four weeks (28 days) of the operation, regardless of cause. The number of patients considered to be immediate surgical mortalities is six (29 per cent) and the histories are summarized as follows:

CASE 16.—Colang., 57 years old. Carcinoma of cervix involving bladder.

Operation: April 3, 1948. Died twenty-two days after operation. Necropsy revealed immediate cause of death to be bilateral ascending pyelonephritis and multiple large pulmonary embolisms. Source of the emboli was the veins of the left leg. Metastases in peri-aortic nodes and in the lungs were found.

CASE 17.—Schrei., 58 years old. Carcinoma of cervix invading bladder. Received irradiation therapy some months previously.

Operation: June 1, 1948. Died five days after operation. Necropsy summary: "The gross and histologic observations offer no definite clue as to the cause of death. No evidence of residual neoplasm."

CASE 18.—Jorgen., 62 years old. Squamous-cell carcinoma of cervix with second primary lesion about urethra. Treated with radium unsuccessfully one year previously.

Operation: Sept. 7, 1948. Convalescence at first uneventful. On tenth day developed chill and rise in temperature to 101° F. Chills recurred almost daily. Blood cultures revealed *Bacillus aerogenes* repeatedly. Expired on twenty-fifth day. Necropsy revealed no residual tumor; there was bilateral acute ascending pyelonephritis with papillary necrosis.

CASE 19.—Cos., 62 years old. Squamous-cell carcinoma of cervical stump previously treated by x-ray. Extensive involvement of bladder and right parametrium.

Operation: May 6, 1948. Died June 4, 1948. Necropsy revealed no evidence of residual neoplasm. There were bilateral hydronephrosis and pyelonephritis (with "necrotizing papillitis, right kidney"). There were multiple abscesses in pelvis and abdominal wall. Survived operation 4 weeks, 1 day.

CASE 20.—Forrest, 49 years old. Squamous-cell carcinoma of cervix diagnosed five months previous to admission and radium application was carried out. Prior to operation extension onto bladder and well into left parametrium was found.

Operation: Aug. 31, 1948. (Operation by Dr. M. J. Jordan.) General condition deteriorated rapidly without apparent assignable cause. Died thirteen days after operation. Partial necropsy revealed ureterocolic implants to be tight and functioning. During post-operative period hypoproteinemia developed and was not rectified. This may have been an important factor in the fatal outcome.

CASE 21.—Sp., 45 years old. Squamous-cell carcinoma of vulva invading anterior vaginal wall and base of bladder. Previous radiation therapy and local excision.

Operation: Jan. 26, 1949. Operation in two stages. After ureteral implantation into colon adequate urinary excretion was present for three days and then ceased. A bilateral nephrostomy was performed. Three weeks later the bladder, vagina, and uterus were resected perineally. Shortly after returning to her room vigorous bleeding occurred from the perineal wound. In spite of reopening and packing the wound the hemorrhage did not cease and the patient died. Necropsy failed to reveal open large vessels. An instance of fibrinoplastic shock (Tagnon and co-workers²).

In four instances where complete necropsies were performed there was no evidence of residual neoplasm. It would appear that an important, if not the most important, factor in the fatal outcome in these patients was sepsis. The significance of the finding of an inflammatory process of varying severity in one or both kidneys at necropsy is debatable. There is undoubtedly an inflammatory reaction in the urinary tract following the procedure as described, which includes bilateral ureterocolostomy. Also, undoubtedly some inflammation existed prior to operation due to partial obstructions of one or both ureters by advancing neoplasm in the pelvis, and, in all probability, these processes when present are aggravated by the operation. Because of the advanced stage of pelvic cancer present and usually with a degree of obstruction in one or both ureters before operation, it is impossible, at least on the basis of the experience here gained, to assess the risk and incidence of pyelonephritis that might complicate bilateral ureterocolic anastomoses.

Among these fatal cases, no patients died during operation. One died of hemorrhage and shock in her room twelve hours after operation. The average survival of the six patients was twelve days after operation.

The immediate surgical mortality in this series is considered to be 28.7 per cent, six among twenty-one patients (death within twenty-eight days of operation—an arbitrarily set criterion). The mortality in a series of forty-eight patients in whom all of the pelvic viscera were excised with implantation of the ureters into the colon was 25 per cent. This would appear paradoxical in that the latter operation is appreciably more extensive than the former but there is no apparent explanation for this fact. Possibly the smaller series which comprises the group reported in this paper accounts for the mortality equal to that of the more extensive operation.

Discussion

Conservation of the rectal colon affords considerable advantages for the well-being of the patient in that a wet colostomy is obviated and control of excreta via the naturally situated colon is much more satisfactory. The operation described above is presented as an alternative surgical attack to complete excision of pelvic viscera upon advanced and uncontrolled cancer of the female genital tract that has invaded the bladder and not involved the rectal colon. It is hoped that continued experience with this procedure will permit of a reduction in the appreciable mortality that obtained in the series presented above. It is to be noted that these are patients selected, not because of a lesion favorable for surgical treatment but who, falling into the category of failures of more conservative measures, are indeed *selected for situations unfavorable for present forms of therapy—radiological or surgical.*

It goes without saying that all of the patients in the series were considered lost by virtue of the stage of disease and that the prognosis was for continued existence, possibly for several months, with all of the disturbances due to progressing advanced pelvic cancer. If the mortality in this group was high, there

is to counterbalance this the fact that the majority of the patients did survive the operation and were rendered *at the moment* free from disease at least macroscopically. Most of them who survived subsequently developed recurrences, after a brief interval, which were rapidly fatal but six (28 per cent) survived sufficiently long to permit the impression that had nothing been attempted they would either be dead of disease at this writing or in the very terminal stages instead of being alive without, momentarily at least, evidence of active disease and without "-ostomies." The immediate salvage rate in this series would not seem negligible.

The latter observation, in the opinion of the writers, has justified the endeavors described above and it is hoped that the initial mortality in the future can be reduced. Radical surgical procedures are always accompanied by high mortality when they are first carried out.

It appears, however, that one tentative conclusion is warranted and that is that in patients who present persistent or recurrent carcinoma of the genital tract with involvement of the bladder following one or several attempts to control the disease by irradiation and/or conservative surgical procedures, a completely defeatist attitude cannot be strongly defended and radical surgical attack, even with its attendant appreciable risks and even without promise of permanent cure, has something definite to offer, at least as being capable of affording a degree of palliation which no other form of management at this time can afford. The relief from pain alone and without creation of a debilitating situation has been a gratifying result in those patients who have survived.

Addendum

Since this report was written, fifteen additional patients have been subjected to the operation, with a surgical mortality as defined above of two patients (13 per cent). In the combined series, therefore, the over-all mortality among thirty-six patients is 22 per cent.

References

1. Brunschwig, A.: Cancer 1: 177, 1948.
2. Tagnon, H. J., Levenson, S. M., Davidson, C. S., and Taylor, F. H. L.: Am. J. M. Sc. 211: 88, 1946.

Zuech, S.: On the Prognostic Value of Sedimentation Rate on Malignant Tumors of the Female Genitalia, Gynecologia 14: 185, 1948.

The author gives a brief review of the literature on the increased sedimentation rate noted in the presence of malignant tumors. He then classifies 250 cases of malignant genital tumors into four categories according to the degree of invasion and then correlates the latter with the amount of increase in the sedimentation rate. The conclusion is that an increase in the sedimentation rate is directly proportional to the amount of invasion of malignant tumors. One must, however, exert a measure of caution and also consider that the sedimentation rate itself is also dependent upon inflammation and secondary anemia, both of which are evident as the malignant neoplasm spreads.

FRANK A. GRACEFFO.

RETROLENTAL FIBROPLASIA: A HAZARD OF PREMATURE BIRTH*†

HAROLD SPEERT, M.D., FREDERICK C. BLODI, M.D., AND ALGERNON B. REESE, M.D.
NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology and the Department of Ophthalmology,
College of Physicians and Surgeons, Columbia University)*

BLINDNESS has recently been added to the recognized hazards of premature birth. Specific pathological alterations may occur in the eyes of infants who are victims of early parturition. These changes ultimately result in the formation of a grayish-white connective tissue membrane in the anterior vitreous. Since the disorder is usually bilateral, useful vision is impaired and partial or total blindness results in most cases. The descriptive name for this condition, "retrolental fibroplasia," coined by Terry, has won almost universal recognition among ophthalmologists. Its clinical and pathological aspects have been described in recent papers by Terry,^{20, 21} Reese and Payne,¹⁸ Krause,¹² and Owens and Owens.¹⁶

Retrolental fibroplasia is not a new disease. Rare cases have been reported from time to time, although called by other names. The past five years have witnessed a tremendous increase in the incidence of this condition. Several possible reasons come to mind in explanation of this rise. One obvious factor is consistent improvement in obstetric and pediatric care, which has resulted in a diminishing neonatal mortality among premature babies, especially the very small ones, almost all of whom were formerly lost. A second possibility, that there has been a true increase in this disorder from unknown causes, remains to be explored. Finally, the rising incidence may be attributable in part to more accurate and more uniform diagnosis, stimulated initially by the writings of Terry.²⁰ For whatever reasons or combinations, the recognized cases of retrolental fibroplasia have mounted so in the last few years that this condition is now believed to be the commonest current cause of blindness in young children.

The etiological factors which result in the strong predilection of retrolental fibroplasia for premature babies are completely obscure. Terry²⁰ has theorized concerning the possible hereditary, prenatal, natal, and postnatal factors, and has concluded that the most probable basis for retrolental fibroplasia is persistence of the hyaloid arterial branches and tunica vasculosa lentis resulting from a precocious increase in blood pressure initiated at birth in adaptation to extrauterine life. Reese¹⁷ has voiced the suspicion that some sort of maternal infection is responsible in these cases, both for the premature labor and for the pathologic changes in the fetal eye, with retrolental fibroplasia appearing as the end stage of the latter.

*This work was supported by a donation from Mr. Charles B. Wrightsman.

†Presented at a meeting of the New York Obstetrical Society, May 10, 1949.

The present study has been planned in an effort to provide basic clinical data, chiefly from the obstetrical standpoint, concerning retrolental fibroplasia, in the hope that this information might help clarify future theorizing and point the way to fruitful lines of investigation. One hundred four pregnancies which have resulted in 110 infants with retrolental fibroplasia, all of whom have been examined by us and whose diagnosis has been verified, form the basis of this study. Actually 190 patients with this diagnosis have been examined by us to date, but many had to be excluded from the present study because of insufficient data. The data have been obtained by means of questionnaires which were submitted to the parents of these children, their obstetricians, and in some cases their pediatricians.

Annual Incidence

The incidence of retrolental fibroplasia, by year of delivery of the 104 patients, is shown in Fig. 1, which covers the past thirteen years, through Dec. 31, 1948. Until 1943, the cases were rare. During the first seven years of this period there was a total of only eight cases, a figure which has been surpassed in each of the succeeding years. The sharp and sustained increase which occurred in 1943 can be correlated with Terry's early papers on the subject. Other possible reasons for the apparent increase in incidence of retrolental fibroplasia have already been mentioned. A final probable factor is the increasing number of patients referred here because of our interest in the disease. The sharp drop for 1948 is only illusory since the necessary time has not yet elapsed, at this writing, for the recognition of the condition in many of the affected infants born during that year.

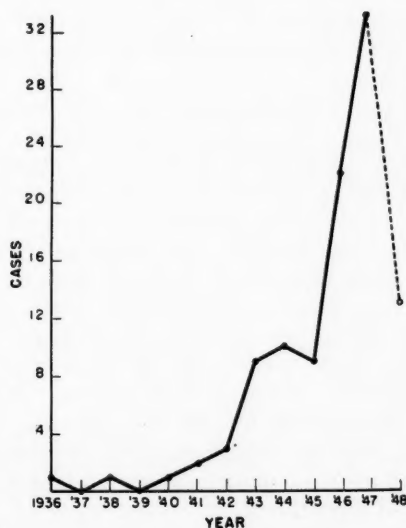


Fig. 1.—Incidence of retrolental fibroplasia by year of birth. Twins are treated as single cases.

Seasonal Incidence

There was no apparent seasonal variation in the incidence of retrolental fibroplasia. The month of birth in our 104 cases is shown in Fig. 2. This agrees with Krause's failure to establish a correlation with month of birth or month of conception in his smaller series of cases. Congenital malformations likewise show no seasonal variation in incidence (Murphy¹⁴).

Geographic Distribution

The birthplace of our patients includes seventeen states, representing all regions of the United States. As might be expected, the heaviest representation comes from New York and its neighboring states, because of their proximity to our institution. Since our series is comprised largely of referred patients, however, no significance can be attached to numerical differences among the various areas of the country.

Fetal Factors

Birth Weight.—The most consistent and impressive anamnestic feature of retrolental fibroplasia is the prematurity of the patient at birth. Ingalls⁹ recorded the mean birth weight of 41 babies as 3.3 pounds (1,497 grams) with a standard deviation of 1.3 pounds (590 grams). The present data are in substantial agreement. All but five of our 110 children were premature, according to the standard criterion of prematurity, a birth weight of less than 5½ pounds (2,500 grams) (Fig. 3). Furthermore, these babies were typically very small at birth, 63 of them weighing not more than 3 pounds (1,360 grams). Survival of the tiniest of such premature infants has been a rarity until quite recently. When Haas⁶ reviewed the literature in 1945, he found records of only 54 infants with a birth weight under 1,000 grams (2 pounds, 3 ounces) who survived. He suggested this weight, therefore, as the lower limit of viability for statistical purposes. Significant numbers of newborns weighing less than 1,000 grams are now being salvaged. It would appear that the incidence of retrolental fibroplasia is roughly inversely proportional to the birth weight of the infant.

The gestation age at birth, recorded for 84 of our infants, is in keeping with their low birth weights (Fig. 4). Less than half were of more than 30 weeks' gestation age and 12 were under 28 weeks, generally accepted as the lower age limit of viability.

Sex and Color.—The sexes were almost equally divided numerically, there being 52 males and 58 females, including twins. It is a rather surprising fact that all the patients in the present series were white. Krause, too, had no Negroes in his series of 18 cases of retrolental fibroplasia, but Owens and Owens recently observed the development of this condition in three Negro babies. Even in our total registry of 190 children with this disorder there are but two Negroes. This disparity assumes greater significance in view of the normally higher incidence of premature birth among Negroes. Congenital malformations, on the other hand, have a higher incidence in whites.¹⁴ Our series consists largely of referred private patients, a fact which is doubtless responsible in part for the paucity of Negroes. Whether a truly significant difference in incidence of retrolental fibroplasia exists between Negroes and whites can be determined by routine ophthalmologic examinations of all premature babies, a study now in progress, as well as by large-scale re-evaluation of the Negro blind of preschool age.

Multiple Births.—Seventeen of the 104 pregnancies (16 per cent) resulted in multiple births, 15 pairs of twins and 2 sets of triplets. Almost half of all twin pregnancies terminate prematurely.⁵ Because of this the incidence of multiple births among prematures is high. In most series the incidence varies between 10 and 12 per cent but it has been reported as high as 23 per cent.¹ Our incidence of multiple pregnancy, therefore, falls within the expected range, since the group is comprised almost exclusively of prematurely born children. The high proportion of multiple births mentioned in previous reports on retrolental fibroplasia^{9, 12, 18} is but a manifestation of the predilection of this abnormality for premature babies.

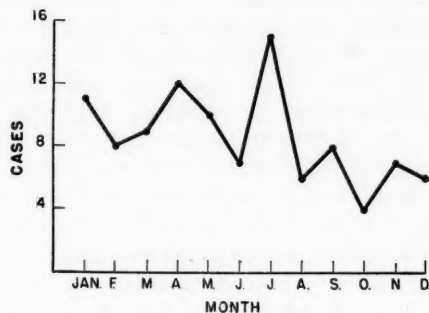


Fig. 2.—Incidence of retrolental fibroplasia by month of birth. Twins are treated as single cases.

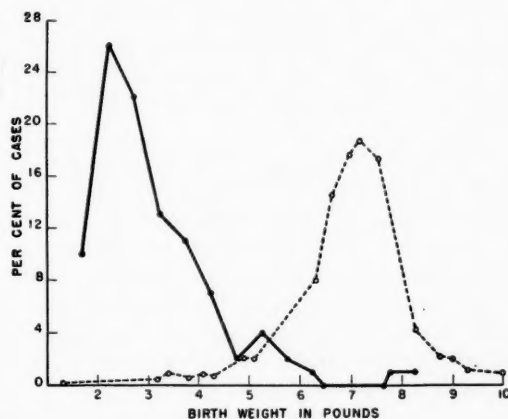


Fig. 3.—Birth weight of infants with retrolental fibroplasia. Broken line shows birth weight of liveborn children in general population. (Adapted from Mitchell-Nelson.¹³)

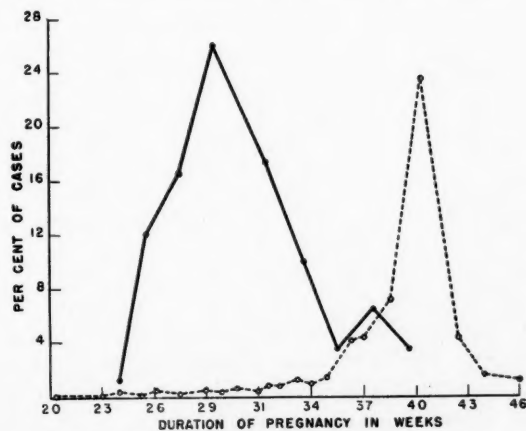


Fig. 4.—Gestation age of infants with retrolental fibroplasia. Broken line shows gestation age of liveborn children in general population. (Adapted from Mitchell-Nelson.¹³)

Both infants developed retrolental fibroplasia in 6 of the 17 cases (including 2 of one of the sets of triplets). Only one of the siblings was affected in each of the remaining 11 cases. In 5 cases of the latter group the affected child was the sole surviving infant. In 4 other cases the children were of opposite sexes, and in one additional instance the children were of the same sex but were definitely reported to be nonidentical. In only one case, therefore, in which both twins survived but only one was affected, does the possibility of homozygosity exist. It has not been possible to obtain further data on this point. This finding is not surprising, since three-fourths of all twin pregnancies are dizygotic, the offspring hence nonidentical.⁴

A striking contrast is afforded by the six pairs of twins in which both infants had retrolental fibroplasia. In each instance both were of the same sex, three pairs being male, three pairs female. Both infants had a common placenta in each of these cases. A confirmatory report that the twins were identical was obtained in three cases. It is of further interest that, in the case of triplets in which all three infants survived, the two with retrolental fibroplasia had a common placenta and were identical twins, whereas the third sibling, which was fraternal, had a separate placenta and was normal.

These observations are too few to warrant generalizations. They suggest, however, that if a twin develops retrolental fibroplasia its homozygous sibling is likely to show the same malformation, while its heterozygous mate is likely to be unaffected.

Associated Abnormalities of Infant and Placenta.—There is a distinct tendency for congenital malformations to be multiple. The common association with retrolental fibroplasia of other abnormalities would therefore add a bit of circumstantial evidence in support of the view that the ophthalmic malformation is already determined at birth. One such abnormality, namely cutaneous hemangiomas, occurred sufficiently often in the children constituting this series to suggest strongly a significant association between retrolental fibroplasia and these vascular tumors. Twelve children had discrete hemangiomas on various parts of the skin, while in four additional patients the vascular malformations were classified as telangiectases. Thus, sixteen of 110 patients with retrolental fibroplasia (15 per cent) also had congenital abnormalities of the cutaneous blood vessels. This figure is significantly higher than the incidence of hemangioma in normal newborns, whether full term or premature.⁸ The nonsurviving twin of another patient had a hemangioma of the brain. Two infants had other malformations of the brain; one, hydrocephalus, the other, cerebral hypoplasia as demonstrated by pneumoencephalogram. Krause has regarded cerebral abnormalities as an important part of the syndrome encephalo-ophthalmic dysplasia, of which retrolental fibroplasia is but one manifestation; but the low incidence of this association (two cases out of 110) makes its significance questionable in the present series. Two other babies had hernias at birth. In two additional cases, blood transfusions were given during the early neonatal period.

The placentas showed no remarkable deviation from the normal for premature babies. In addition to the four cases of premature separation which were associated with bleeding and were diagnosed clinically before delivery, one patient (with twins) had abruptio placentae without external bleeding, and the placentas of four other patients showed evidence of some degree of premature separation when examined post partum. One placenta had a marginal insertion of the cord.

Parental Factors

Parental Age.—The mothers varied in age between 18 and 41 years at the time of birth of the affected infants. Their age distribution, shown in Fig. 5,

conforms fairly well to the maternal age distribution curve for the entire U. S. birth registration area. The slight shift to the right of the curve for the mothers in the present series may be attributable to its being rather heavily weighted with patients of a higher than average economic level. Murphy¹⁴ has noted a statistical relation between increasing maternal age and the incidence of congenital malformations in the offspring, but no such correlation can be made from our data.

The corresponding ages of the fathers ranged between 20 and 54 years, this factor likewise showing no relation to the incidence of retrolental fibroplasia in the infant. The difference in parental ages (paternal age minus maternal age) covered a span of twenty-seven years, varying from plus 24 to minus 3, with more than half of the cases grouped between plus 3 and 0 (Fig. 6). Obviously, therefore, parental age bears no significant relation to retrolental fibroplasia in the offspring.

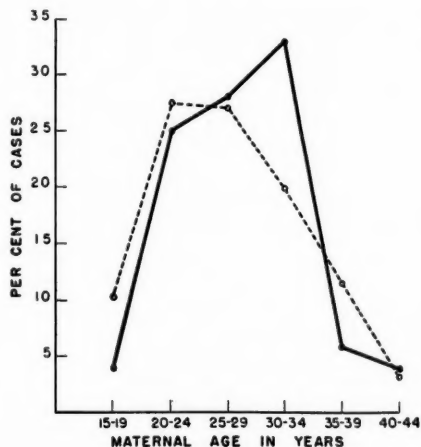


Fig. 5.

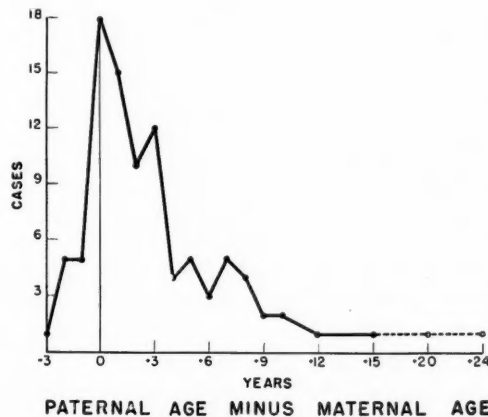


Fig. 6.

Fig. 5.—Age of mothers of infants with retrolental fibroplasia. Broken line shows maternal age distribution for U. S. Birth Registration Area, 1945.

Fig. 6.—Difference in parental ages in cases of retrolental fibroplasia. Twins are treated as single cases.

Parity of Mother, Previous and Subsequent Obstetrical History.—Previous obstetrical history of the mother was unrelated to the development of retrolental fibroplasia in the child. Fifty-one of the mothers in this series had never been pregnant before, whereas 53 had experienced one or more pregnancies. The number and outcome of these pregnancies are shown in Table I. Twenty-one of the women had had a total of 27 previous miscarriages. Nineteen women had had 22 premature babies previously. Three had had one stillbirth each. Forty-six had 74 living children from prior pregnancies.

About one-fourth of the mothers have had further pregnancies subsequent to the birth of the affected child. In five pregnancy was in progress at the time of this writing. The results of the completed subsequent pregnancies are summarized in Table II. Five had a miscarriage. Six had another premature baby. One had a stillbirth. Fourteen subsequently gave birth to a total of twenty living children.

Both the past and subsequent obstetrical histories of the mothers of children with retrolental fibroplasia showed a higher incidence of miscarriage and of premature parturition than would be expected in a random sample of parous women. This is in accord with the experience of Murphy and Bowman¹⁵ and with the statistical observations of Gardiner and Yerushalmy,² who

showed a familial susceptibility to prematurity, to the extent that premature parturition tends to be repetitive, and that mothers who have previously had a premature labor or miscarriage are more likely to have a premature birth in a succeeding pregnancy than mothers who have had only full-term infants before.

TABLE I. OBSTETRICAL HISTORIES OF MOTHERS PRIOR TO BIRTH OF AFFECTED CHILDREN

PARITY	MISCARRIAGES	PREMATURES	STILLBIRTHS	LIVING CHILDREN
0	83	85	101	58
1	17	16	3	26
2	2	3	0	12
3	2	0	0	8
	104	104	104	104

TABLE II. OBSTETRICAL HISTORIES OF MOTHERS SUBSEQUENT TO BIRTH OF AFFECTED CHILDREN

PARITY	MISCARRIAGES	PREMATURES	STILLBIRTHS	LIVING CHILDREN
0	99	98	103	90
1	5	6	1	8
2	0	0	0	6
	104	104	104	104

There is nothing in the present data, however, to suggest a tendency to repetition of retrolental fibroplasia in a subsequent child, following the appearance of this defect in one member of a family. On the contrary, there has been no instance in this series in which retrolental fibroplasia has been observed in any two members of the same family other than twins. This is in striking contrast to the tendency of congenital malformations to recur in siblings.

Complications of Pregnancy.—

Bleeding: The commonest complication of pregnancy in the mothers comprising the present series was vaginal bleeding. The frequency of this symptom in association with retrolental fibroplasia in the offspring has been commented upon previously.^{9, 18} More than one-fourth of the mothers noticed bleeding, varying in time and amount, during their pregnancy. The distribution of these patients, by stage of pregnancy and amount of bleeding, is shown in Table III. In about one-half of these cases bleeding was confined to the first trimester and consisted of mere staining. Five of the eight patients who complained of bleeding during the second trimester also had this symptom later (not shown in table).

The cause of the bleeding was not ascertained in nineteen of the cases. Four had partial placenta previa, an equal number premature separation of the placenta, two had a threatened abortion, and one a cervical polyp.

At first glance the incidence of these complications would seem unexpectedly high. When it is recalled, however, that we are dealing with a selected group of cases, heavily weighted with prematurely terminated pregnancies, this observation loses much of its significance. Anderson and Lyon,¹ who reviewed the literature on the causes of prematurity, found the reported incidence of unexplained vaginal bleeding to vary between 1.2 and 18.2 per cent, the incidence of placenta previa between 1.3 and 9.0 per cent, and of premature separation of the placenta between 1.3 and 5.0 per cent. Our incidence of these conditions falls within the above limits. There is no reason for believing, therefore, that maternal bleeding complications are more common in pregnancies associated with retrolental fibroplasia than in other pregnancies terminating prematurely.

TABLE III. VAGINAL BLEEDING DURING PREGNANCY

MONTH	NO. OF CASES	BLEEDING		
		SLIGHT	HEAVY	UNSPECIFIED
1-3	13	13	0	-
4-6	8	2	2	4
6+	9	2	2	5
Total	30			

One additional patient complained of rectal bleeding throughout pregnancy, but its source was never investigated.

Infections: Clinically recognizable infections were present during pregnancy in twelve of the mothers. Nine were respiratory infections, two rubella, and one a local dental infection. Eight of the infections occurred during the first four months of pregnancy (Table IV). Particular interest attaches to the two cases of rubella because of the common association of German measles in pregnancy with congenital malformations, especially cataract, in the offspring. One of the patients acquired rubella in the second month, the other in the eighteenth week of pregnancy. Neither infant showed any abnormality other than retrolental fibroplasia.

TABLE IV. TIME OF MATERNAL INFECTION

MONTH OF PREGNANCY	NO. OF CASES
2nd	2
3rd	1
4th	5
7th	1
8th	2

The incidence of maternal infections, particularly those of the upper respiratory tract, seems abnormally low. It is likely that some of the milder colds were either forgotten or were considered unworthy of reporting on the questionnaires.

Puerperal infections were recorded for only two of the mothers. One patient had postpartum pyelitis, and the other developed thrombophlebitis following a cesarean section. Thus there appears to be no significant association between retrolental fibroplasia and maternal infection during pregnancy or the puerperium, with the possible exception of rubella.

TABLE V. OTHER MATERNAL COMPLICATIONS

DIAGNOSIS	NO. OF CASES
Asthma	1
Diabetes	1
Gastrointestinal upset	3
Hydramnios	2
Intervertebral disc herniation	1
Premature rupture of membranes	7
Pruritus, unexplained	1
Surgical operations	3
Toxemia of pregnancy	8
Trauma	7
Ulcerative colitis	1
Uterine tumor	1

Other Maternal Complications: Twelve other maternal complications of pregnancy are listed, together with their incidence, in Table V. Asthma, diabetes mellitus, ulcerative colitis, and a herniated intervertebral disc antedated the pregnancy of four patients. The three surgical operations con-

sisted of the removal of an ovarian cyst at 22 weeks, and two dental extractions. The seven cases of trauma all consisted of falls, two in the fourth month, two in the seventh month, one in the eighth month, and two not dated. The incidence of toxemia of pregnancy and of premature rupture of the membranes were well within expected limits. The frequency of these miscellaneous conditions is neither higher than would be anticipated in a group of pregnancies which terminated prematurely nor do these complications present any pattern which suggests a possible etiological relation to retrolental fibroplasia in the offspring.

Medication During Pregnancy and Labor.—The possibility has been suggested that drugs administered during pregnancy might in some way affect the fetal eye and so serve as a factor in the development of retrolental fibroplasia.²⁰ About one-half of the mothers in this series received supplementary vitamins, calcium, and iron, alone or in combination during their pregnancy. These substances are in such widespread routine use nowadays, however, that this incidence is without significance. A few patients were treated with estrogens, progesterone, and vitamin E, as shown in Table VI, and one each received insulin, a sulfonamide, penicillin, and the antihistaminic drug Benadryl.

The frequency with which analgesic drugs were prescribed during labor is rather surprising, in view of their well-known depressing effect on the fetal respiratory center. The most commonly used analgesics were the barbiturates, scopolamine, and Demerol, as shown in Table VII. In 36 of 99 cases, however, no drugs were given for relief of pain prior to delivery. Analgesic medication during labor seems, therefore, unrelated to the pathologic process in the eyes of the offspring.

TABLE VI. MEDICATION DURING PREGNANCY

	NO. OF CASES*
Vitamins, calcium, iron	50
Estrogen	4
Progesterone	5
Vitamin E	4
Insulin	1
Sulfonamide	1
Penicillin	1
Benadryl (Parke, Davis & Co.)	1
None	21

*Data on 88 cases.

TABLE VII. ANALGESICS DURING LABOR

	NO. OF CASES*
None	36
Barbiturates	22
Scopolamine	17
Demerol	16
Morphine	3
Paraldehyde	2
Pantopon	2
Caudal	1

*Data on 99 cases.

Onset of Labor.—Information was provided concerning the onset of labor for 89 patients. In 79 cases labor began spontaneously; in three labor was induced; and seven patients were delivered by elective cesarean section without any labor. In ten cases, therefore, the infants were born prematurely only

because of the obstetrician's intervention. That these babies developed retrolental fibroplasia would seem to relate the disease to prematurity per se rather than to a hypothetical common cause, such as infection, of premature labor and retrolental fibroplasia.

Type of Delivery.—More than half of the infants were born spontaneously with vertex presentation. Forceps were used for 20 of 93 infants. Eleven delivered by the breech, seven by cesarean section, and three by version and extraction. While method of delivery is of great importance in the survival of premature babies, this factor is obviously of no significance in the etiology of retrolental fibroplasia.

Blood Serology and Rh Factor.—The serologic test for syphilis was negative in all mothers but one. The Rh factor was reported for 40 mothers, 36 of whom were Rh positive. Of the four Rh-negative women, two were known to have Rh-positive husbands. Both patients were primigravidas, and neither showed Rh antibodies during pregnancy, nor did the offspring have any stigmas of erythroblastosis.

Discussion

The etiology of retrolental fibroplasia still remains obscure. The only progress that has been made in this direction has consisted of the elimination of some of the theoretically possible factors which Terry enumerated in 1943. In addition to the broad categories of hereditary and environmental influences and the various causes of prematurity, Terry mentioned as possibly important the use of new drugs; trauma resulting in intraocular hemorrhage; incomplete homothermism; premature exposure to light; premature loss of materials previously supplied through the placenta; incomplete digestion and assimilation of foodstuffs, resulting in deficiencies, in riboflavin, for example; anemia of prematurity; and isoimmunization caused by Rh incompatibility.

The theory considered most plausible by Terry, ascribing importance to the precocious increase in blood pressure caused by premature birth, was later abandoned by him because of physiologic and pathologic objections. More recently, in unpublished experiments, Krause has found premature exposure to light to be irrelevant, since the eye abnormality has manifested itself in premature infants raised in darkness. The possible importance of a maternal vitamin A deficiency was suggested by experiments of Warkany and Schraffenberger²³ who found a fibrous retrolenticular membrane in the eyes of newborn rats the mothers of which had been on vitamin A deficient diets. Jackson and Kinsey¹⁰ later demonstrated, however, that these vascular defects in the young rat occurred only when the degree of vitamin A deficiency in the mother was so severe that normal birth was interfered with and fetal resorption was common. They considered it unlikely, therefore, that this vitamin deficiency was the sought for cause of retrolental fibroplasia in the human.

Ingalls,⁹ impressed with the high incidence of placenta previa and of placental hemorrhage in pregnancies resulting in retrolental fibroplasia in the child, has suggested an "abnormal placental environment" as the etiologic factor. We join with others in questioning the adequacy of Ingalls' controls and believe his conclusion to rest on a rather insecure statistical foundation.

The present observations serve to dispel several additional etiological possibilities. No important seasonal or obvious geographic factors affected the incidence of retrolental fibroplasia in this series. Parental ages and the difference between them likewise seem irrelevant. No relation exists between retrolental fibroplasia in the offspring and parity of the mother. The parous women had a higher than normal incidence of miscarriage and premature

labor in other pregnancies, but this is to be expected because of the tendency of these complications to recur. The high incidence of bleeding and of placental abnormalities lacks direct etiological significance, since they fall within the limits observed in other studies of premature delivery. These complications were associated primarily with the premature parturition rather than with the retrolenticular changes in the infant. Similarly, clinical infection in the mother, with the possible exception of rubella, bore no apparent relation to the development of the abnormality in the infant. It has been suggested that a hypothetical subclinical infection during pregnancy might have been responsible for both the premature onset of labor and the developmental anomaly in the eyes of the fetus. A potent objection to this possibility is the fact that in a significant proportion of the cases labor was not spontaneous but was either artificially induced or the patient was delivered by elective cesarean section. Serologic tests of maternal blood have eliminated syphilis and Rh incompatibility as factors in the etiology of retrolental fibroplasia. Our data likewise have shown the lack of significance of maternal medication during pregnancy and labor and of type of delivery.

The single and most consistent clinical concomitant of retrolental fibroplasia is the history of premature birth. In a general way the incidence of the disorder seems inversely related to the birth weight of the child. Still unsettled is the question whether the eye changes occur for the first time in the neonatal period or whether they are truly congenital and present at birth but undetectable by the usual ophthalmoscopic examination because of their location at the periphery of the fundus oculi.

There is circumstantial evidence both in support and in contradiction of the view that retrolental fibroplasia is a congenital malformation. Consistent with the theory of its congenital nature is its apparently higher frequency among whites than Negroes, its association with prematurity, and the high degree of coincidence with another congenital abnormality, namely cutaneous hemangiomas and telangiectases. In one case the ocular condition was recognized at birth by two physicians.

Our concept of the nature and mechanism of production of congenital malformations continues to enlarge. In addition to the importance of genetic factors we now recognize the possibility that such defects may be produced, at least experimentally, by a variety of environmental factors including radiant energy, maternal dietary deficiencies, maternal infection, and the injection of nitrogen mustard⁷ or trypan blue³ into the mother during pregnancy.

Highly suggestive of a genetic influence in retrolental fibroplasia is the apparent tendency of the abnormality to occur in identical twins but not in fraternal twins. A strong objection to its genetic basis, however, is its failure to recur in the same family. There is no recorded instance in which a mother has produced more than one child with this disorder in separate pregnancies, although Dr. V. Everett Kinsey¹¹ has recently encountered two such siblings.

These data suggest the interaction of several factors in the pathogenesis of retrolental fibroplasia. Foremost is prematurity. Of less obvious importance are probable genetic factors and possible environmental ones, such as in the occasional case of maternal rubella.

Estimates of the incidence of retrolental fibroplasia vary in different regions but all investigators are agreed that the incidence is highest among the children who were smallest at birth. It has been estimated that about 13 per cent of all infants with a birth weight of four pounds or less show clinical evidence of this abnormality and most of them are blind. Some more recent estimates are even higher. There is no satisfactory treatment for retrolental fibroplasia. Practical clinical efforts must therefore be aimed at prevention

through the prevention of premature birth. In subsequent observations confirm current impressions concerning the high incidence of blindness from this cause in the very tiny prematures, it may be necessary to modify our views as to the justifiability of attempts to raise all of these infants.

Summary

1. A clinical study is reported of one hundred four pregnancies which resulted in the development of retrolental fibroplasia in the offspring.
2. The incidence of this disorder appears to be on the rise.
3. No seasonal or geographic influence could be demonstrated.
4. Ninety-six per cent of the affected children were born prematurely.
5. The sexes of the children were about equally divided, but all were white.
6. Seventeen of the pregnancies resulted in multiple births, including two sets of triplets. There is a strong indication that in all monozygotic pregnancies both children were affected, while only one was affected in the dizygotic pregnancies.
7. Cutaneous hemangiomas were associated with retrolental fibroplasia in a proportion of cases significantly higher than the expected incidence.
8. Parental ages or the difference between them was of no significance.
9. Parity of the mother and her previous and subsequent obstetrical history were of no direct significance. The relatively high incidence of miscarriage and of premature delivery in other pregnancies is a manifestation of the tendency of premature labor to be repetitive.
10. The incidence of bleeding complications during pregnancy was within the limits for premature birth.
11. Maternal infections and other complications during pregnancy, with the possible exception of rubella, had no etiological relation to retrolental fibroplasia in the child.
12. Similarly irrelevant were maternal medication during pregnancy and labor, whether labor was spontaneous or induced, type of delivery, maternal serologic test for syphilis, and her Rh factor.
13. In addition to the obvious role of prematurity, available evidence suggests the probable importance of genetic factors, and occasionally environmental factors such as maternal rubella, in the etiology of retrolental fibroplasia.
14. Since no satisfactory treatment is known for retrolental fibroplasia, efforts at reducing its incidence must lie primarily in the prevention of premature birth.

References

1. Anderson, N. A., and Lyon, R. A.: *Am. J. Dis. Child.* **58**: 586-594, 1939.
2. Gardiner, E. M., and Yerushalmy, J.: *Am. J. Hyg.* **30**: Sec. A: 11-31, 1939.
3. Gillman, J., Gilbert, C., Gillman, T., and Spence, L.: *S. African J. M. Sc.* **13**: 47-90, 1948.
4. Guttmacher, A. F.: *AM. J. OBST. & GYNEC.* **34**: 76-84, 1937.
5. Guttmacher, A. F.: *AM. J. OBST. & GYNEC.* **38**: 277-288, 1939.
6. Haas, R. L.: *AM. J. OBST. & GYNEC.* **50**: 406-411, 1945.
7. Haskin, D.: *Anat. Rec.* **102**: 493-513, 1948.
8. Hess, J. H., Mohr, G. J., and Bartelme, P. F.: *The Physical and Mental Growth of Prematurely Born Children*, Chicago, 1934, University of Chicago Press.
9. Ingalls, T. H.: *J. A. M. A.* **138**: 261-263, 1948.
10. Jackson, B., and Kinsey, E.: *Am. J. Ophth.* **29**: 1234-1241, 1946.
11. Kinsey, V. E.: Personal communication.
12. Krause, A. C.: *Arch. Ophth.* **36**: 387-444, 1946.
13. Mitchell-Nelson: *Textbook of Pediatrics*, Philadelphia, 1946, W. B. Saunders Company.

14. Murphy, D. P.: *Congenital Malformations*, ed. 2, Philadelphia, 1947, J. B. Lippincott Company.
15. Murphy, D. P., and Bowman, J. A.: *AM. J. OBST. & GYNEC.* 24: 273-276, 1932.
16. Owens, W. C., and Owens, E. U.: *Am. J. Ophth.* 32: 1-21, 1949.
17. Reese, A. B.: *Am. J. Ophth.* 31: 623-625, 1948.
18. Reese, A. B., and Payne, F.: *Am. J. Ophth.* 29: 1-18, 1946.
19. Terry, T. L.: *Arch. Ophth.* 29: 36-53, 1943.
20. Terry, T. L.: *Arch. Ophth.* 29: 54-65, 1943.
21. Terry, T. L.: *Arch. Ophth.* 33: 203-208, 1945.
22. Statistical Abstract of the United States, 1947, U. S. Bureau of the Census.
23. Warkany, J., and Schraffenberger, E.: *Arch. Ophth.* 35: 150-169, 1946.

Campbell, Kate: Intracranial Disorders of the New-Born Associated With Birth, M. J. Australia 2: 57, July 17, 1948.

The author divides these intracranial disorders related to birth into three headings: (1) intracranial hemorrhage; (2) anoxemia—asphyxia, apnea, hypoxemia; (3) fracture of the skull. As the skull passes through the birth canal, the falx and tentorium which are unyielding structures, may tear, if stretched beyond the limits of their elasticity. Tentorial tear is estimated by some authors to be responsible in over 92 per cent of the deaths from intracranial hemorrhage. Intracranial hemorrhage is frequently accompanied by anoxemia. There are four types of intracranial hemorrhage:

1. Subdural
2. Extradural
3. Subarachnoid
4. Intraventricular

The subdural is the commonest type of hemorrhage.

Methods of treatment such as oxygen, tracheal catheter, resuscitation, etc., are enumerated and discussed. Atelectasis and pneumonia are the brief causes of death. Treatment consists chiefly of vitamin K, lumbar puncture, oxygen, and sedation to combat restlessness.

WILLIAM BERMAN.

Weymuller, Charles A.: Practical Measures for the Reduction of Mortality From Premature Birth, Westchester M. Bull. 17: 13, 1949.

The author reviews the contributions which the obstetrician and pediatrician can make to the improvement in mortality from prematurity. He outlines the obstetrical measures recommended by Beck which include careful supervision of normal pregnancy, prompt care of abnormalities like heart disease and syphilis in pregnancy, and full use of all means to prevent fetal trauma in labor. These include preservation of the membranes, elimination of depressing analgesics and anesthetics, use of vitamin K, episiotomy, and prevention of chilling of the newborn infant.

In his outline of the pertinent pediatric measures, the importance of warmth and oxygen in the delivery room and during the first 24 hours is stressed. The author then goes on to present the small-unit nursery techniques, individual assignment of nurses, elimination of central supply room, and isolation principles which have proved very efficient in his hospital for they have resulted in a 30 per cent improvement in the premature mortality rate.

S. B. GUSBERG.

VALUE OF X-RAY THERAPY IN AMENORRHEA AND STERILITY ASSOCIATED WITH ENDOMETRIAL HYPERPLASIA

SAMUEL A. WOLFE, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Long Island College of Medicine)

ENDOMETRIAL hyperplasia designates pathological overgrowth of endometrial glands, stroma, and blood vessels resulting from prolonged or excessive estrogenic stimulation. The classical "Swiss cheese" pattern of the endometrium, and its subtypes of simple follicular and advanced adenomatoid hyperplasia, have been emphasized by Novak. The lesion results from persistent and/or excessive numbers of follicular cysts in the ovary. Corpora lutea are not formed. Reproduction of the lesion in the human castrate by large doses of estrogen proves this concept. Hyperplasia associated with granulosa and theca-interna tumors of the ovary points in the same direction.

Abnormal uterine bleeding is the prime clinical symptom of hyperplasia. The disease may occur at any age. A puberal group has been clinically defined, but premenopausal incidence is dominant. Not sufficiently emphasized, however, is the paradox that endometrial hyperplasia also produces amenorrhea, hypomenorrhea, and frequently, alternating episodes of prolonged amenorrhea followed by bleeding of varied duration. Sterility is an obvious symptom in a lesion in which ovulation does not occur. Since bleeding is only occasionally the result of demonstrable thrombosis in the subepithelial capillaries of the hyperplastic endometrium, it has been assumed that this symptom is usually due to a fall in the estrogen level of the blood. Conversely, when a constant estrogen blood level is maintained, amenorrhea is the predominant manifestation. The liver plays an important role in the metabolism of estrogens, but the mechanism is not fully known.

In differential diagnosis of endometrial hyperplasia, vaginal bleeding appearing after amenorrhea requires exclusion of uterine or tubal gestation. "Irregular shedding of the endometrium," too, is associated with amenorrhea followed by prolonged bleeding. The persistence and continued function of the corpus luteum in this entity has been emphasized by Brewer and Jones and also by McKelvey and Samuels. In the nonbleeding phase, "polyhormonal amenorrhea," associated with hyperplasia, requires exclusion of systemic factors as anemia and low blood protein levels. In the endocrine field, hyper- and hypothyroidism are causes of amenorrhea. Basophilic adenoma of the pituitary, suprarenal cortex adenoma or hyperplasia are also to be considered. Ovarian failure with amenorrhea is established by complaints of flushes, nervousness, weight gain, and is readily confirmed by vaginal smears and endometrial biopsy. High urinary gonadotropin in the absence or reduction of estrogens is a classical finding in ovarian failure. Pituitary amenorrhea, on the contrary is associated with low gonadotropic and estrogen values in the urine. The endometrial bi-

opsy and vaginal smear are accessory aides. In glandular-cystic hyperplasia with amenorrhea, the gonadotropic values in blood and urine are generally low, but estrogen values in blood and urine show no distinctive pattern. The vaginal smear shows a persistently high number of flat squamous cells. Clinically, the uterus is normal or slightly enlarged and the ovaries, too, are often enlarged and even cystic. The absolute diagnosis of amenorrhea due to endometrial hyperplasia is readily established by histologic study of an endometrial biopsy or curettings.

Therapy of the amenorrheic form of hyperplasia is difficult. From a physiological viewpoint, pituitary extract with follicle-stimulating and luteinizing factors would be ideal, but no such preparation is available. Lutein or luteinizing hormones as progesterone or chorionic gonadotropic hormone, though seemingly useful to further metabolism of, and the excess of estrogen, do not relieve amenorrhea. Pregnant mare serum and Synapoidin (a pituitary-like preparation with follicle-stimulating potentialities) followed by, or in combination with, chorionic gonadotropin or progesterone are seldom productive of results. Cyclic priming by estrogens followed by progesterone, as employed by Hamblen in the bleeding type of hyperplasia, requires further evaluation as an established cure in the amenorrheic type of hyperplasia. The inhibition of normal pituitary function by excessive amounts of estrogen from the persisting granulosa cysts has been removed by block extirpation of cysts from the ovary resulting in subsequent relief of amenorrhea.

A similar result can be more safely accomplished by destruction of the granulosa cysts exposed to x-ray radiation. In 1926, I. C. Rubin reported the value of x-ray therapy in cases of amenorrhea associated with large ovaries. In the same year, I. S. Hirsh also used this agent for treatment of amenorrhea. Further contributions were made by L. Edeiken, and I. I. Kaplan in large series of cases. The latter reported 296 cases of amenorrhea and sterility treated by x-ray administered to the ovary and pituitary. Of these, 171 subsequently had normal menses and 90 became pregnant. All had children free from defects. Seventy others could not be followed and 55 patients failed to respond. Unfortunately, the necessary endocrinological data are not given, and so the type of amenorrhea treated is not known. In a more recent report, D. G. Drips emphasized low-dosage irradiation of the ovaries empirically in both ovarian and pituitary amenorrhea. Among 331 cases reported, there were 136 single women. Of these, 63 were primarily pituitary in type and 73 were primarily ovarian. In 46 of the 63 pituitary cases, normal menses followed and in the ovarian group 48 patients had return of a normal cycle. Good results were obtained also in 123 married women similarly treated and of these 34, or 27.6 per cent, became pregnant. However, in many of the cases reported in this series, amenorrhea was of short duration and others were first improved by the use of thyroid extract or by cyclic priming of the endometrium.

Gynecologists generally have not endorsed x-ray therapy of amenorrhea because of: (1) Fear of ovarian damage by x-radiation. This is certainly true, if amenorrhea is of the ovarian type, for here even low dosage may further suppress or damage primordial follicles. However, it is not uncommon for such patients to persist in the amenorrheic phase even if untreated, and so a poor result could be wrongfully assigned to x-ray therapy. (2) Fear of abnormalities in the offspring. This is not supported by observation of the babies in the series reported by Edeiken and Kaplan. Whether mutation and congenital malformations may appear in later generations as result of radiation injury to chromosomal genes cannot be told. The experiments by H. J. Muller with the fruit fly strongly indicate such a possibility. E. G. Anderson of the California Institute of Technology showed the radiation effects on the second generation

of corn grown from seeds exposed at Bikini. Many ears were no more than half developed and the kernels were off-color and malformed. This was ascribed to the disturbance produced in the system of genes and chromosomes.

From the above it would appear that radiation of human ovaries should be employed therapeutically only after all other methods have been proved unsuccessful. J. Hoffman holds the same viewpoint. In the three cases described below, amenorrhea and sterility were the prime complaints of endometrial hyperplasia for which x-ray was employed. Endometrial biopsies before and after radiation allowed studies of the morphological changes in the endometrium following the use of this agent. With return of normal morphology and function, two patients became pregnant and delivered normal children. The third had prompt return of menses from a proved secretory endometrium, but pregnancy has been voluntarily excluded by contraception.

CASE 1.—Miss L. S., aged 23 years, seen Dec. 1, 1938, complained of infrequent menses. The family and past personal history were irrelevant. Menses appeared belatedly at the age of 17 years and only seven bleeding episodes appeared in the six years since the onset of the menarche. The last two periods occurred in October, 1937, and April, 1938. The general physical examination was negative except for mild hirsutism of the face and extremities. The weight was 115 pounds, height 168.2 cm., and the span 168.75 cm. The breasts were small. Rectal palpation (virginal state) showed a pubescent uterus with a long cervix and a small body. The adnexa were negative. X-ray of the skull showed a normal sella turcica. The basal metabolism rate was -18 per cent. The blood count was normal. Urine assay for hormones revealed the absence of gonadotropins, and a low estrogen level (2 R.U.), indicating pituitary amenorrhea in association with hypoplasia of the genitals. The patient was placed on high-protein diet, outdoor exercises, and extract thyroid, $\frac{1}{2}$ grain three times a day. This regime was instituted on Dec. 30, 1938. On Feb. 2, 1939, vaginal bleeding appeared and continued irregularly until Feb. 25, 1939. On March 12 and 13, there was recurrent bleeding, as also on April 2, April 8, and April 15 to 16. The bleeding phase of glandular cystic hyperplasia was now suspected and progesterone 15 mg. was given empirically on alternate days for four doses, with cessation of bleeding. A supposedly normal period followed May 9 to 14, but staining occurred June 2 and continued daily until June 23. For the remainder of the year 1939, the patient continued with prolonged and irregular episodes of amenorrhea followed by intermittent staining or bleeding. The physical findings remained unchanged. A repeated basal metabolic rate test showed a reading of -12 per cent. The patient married Jan. 2, 1940. Endometrial biopsy on Jan. 9, 1940, confirmed the revised diagnosis of glandular cystic hyperplasia (Fig. 1). Intermittent staining from January 15 to February 15 was not influenced by a second course of progesterone. Endometrial biopsy repeated on February 28 showed persisting hyperplasia. Bleeding continued irregularly during March and a third biopsy April 18, 1940, showed no change in the endometrial pattern. Estrogen 30,000 I.U. plus progesterone 10 mg. for 4 doses arrested the bleeding. Amenorrhea now reappeared. Examination on September 17 showed a uterus of almost normal size but the right ovary was cystic and about three times its normal size. Thyroid extract was resumed, and bleeding episodes occurred Dec. 19 to 26, 1940, and March 4 to 9, 1941. There was no further bleeding for eleven months i.e., February 17 to 23, 1942. Another bleeding episode followed from May 24 to June 1, 1942, to be succeeded by amenorrhea which lasted until Feb. 25, 1943. There were three additional bleeding episodes on May 5 to 10, Aug. 2 to 7, and Nov. 8 to 13, 1943. The general physical and pelvic examination was unchanged. In 1944, bleeding appeared January 11 to 14. A fourth endometrial biopsy on January 21, (Fig. 2) showed persisting glandular-cystic hyperplasia with adenomatoid foci. Bleeding episodes followed with some regularity from Feb. 18 to Nov. 6, 1944, to be followed by amenorrhea. Examination on Feb. 11, 1945, showed no changes in the pelvis. The basal metabolic rate was found normal and the fifth biopsy on the same date showed persistent glandular hyperplasia. Synapoidin was administered and the course of 10 injections was

Fig. 1.

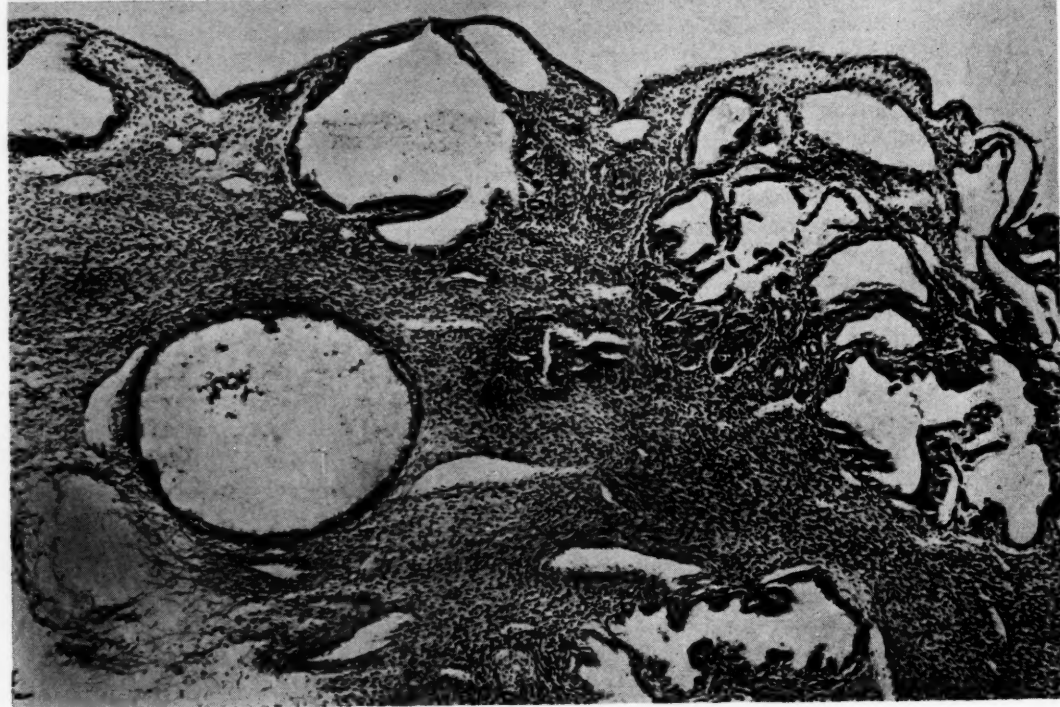
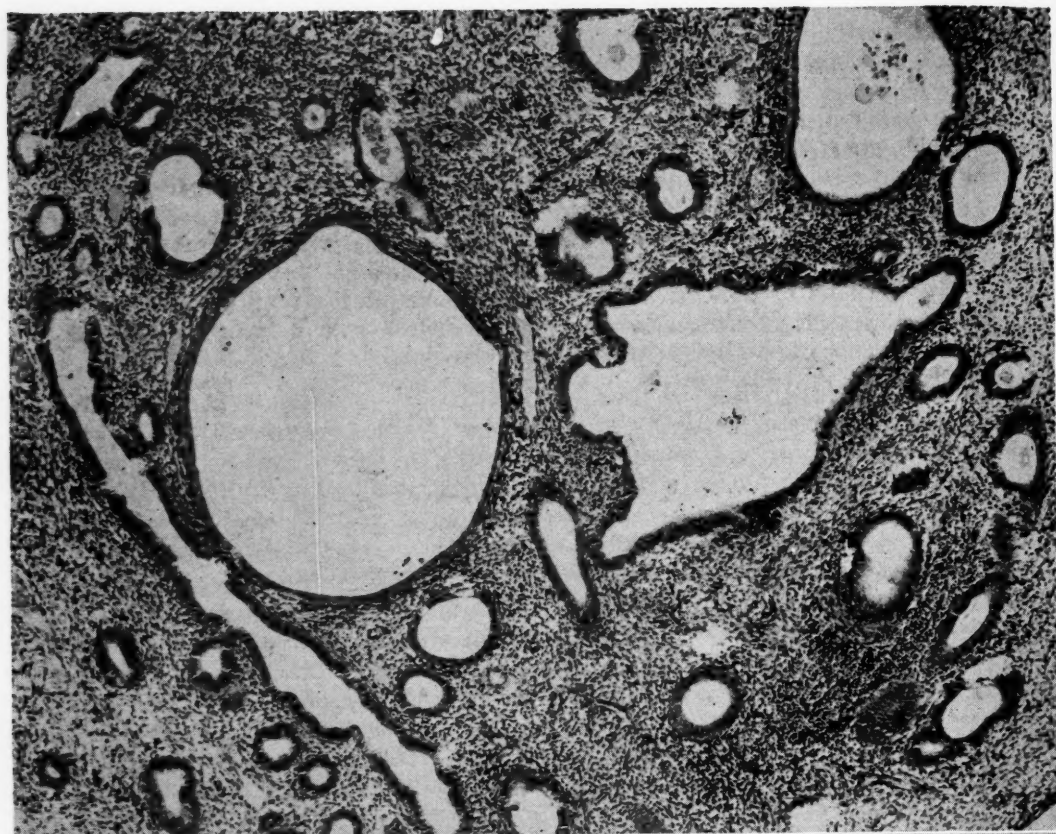


Fig. 2.

(See legends on opposite page.)

completed on Feb. 24, 1945, without result. X-radiation to the pituitary was accordingly advised. A right lateral and left lateral port (6 by 8 cm.) was employed, and 150 r. units were administered to each side on March 21, March 25, April 2, and April 4, 1945, for a total dose to the pituitary fossa of 800 r. units. The factors were 200 kv., 4 ma. current; 2 mm. Cu., and 1 mm. Al. This was of little value. On June 19 after seven months of amenorrhea, staining appeared. A biopsy (the sixth) on the same day showed glandular-cystic hyperplasia, but a seemingly functional stroma showed formation of a compacta about the spiral arterioles, thus indicating antecedent ovulation (Fig. 3). The anticipated menses failed to appear and amenorrhea persisted. As a last resort x-ray to the ovaries was administered by Dr. Ira Kaplan between Sept. 4 and Sept. 28, 1945. High voltage x-ray was employed. The factors were 200 kv.; 4 to 5 Ma., with 0.5 mm. Cu. plus 1 mm. Al. as filter. The target distance was 50 cm. Right and left anterior and posterior ports 9 by 12 cm. were used and 50 to 75 r. (measured in air) were given at weekly intervals for three weeks. The pelvis was irradiated anteriorly the first week, posteriorly the second week, and again anteriorly the third week. A bleeding episode occurred October 28 to November 2. On November 29, the breasts were noted as full and an Aschheim-Zondek test on December 1 was reported as positive. Unfortunately, complete spontaneous abortion occurred on December 15. Examination December 29 showed a small well-involuted uterus. In 1946 menses occurred regularly every 26 to 28 days. The seventh biopsy on August 23 (twenty-second day of cycle) showed a normal endometrium in the early premenstrual phase (Fig. 4). The last period prior to gestation occurred October 23 to 27, and an Aschheim-Zondek test was reported positive, Nov. 30, 1946. The subsequent pregnancy was without incident. On July 24, 1947, there was spontaneous delivery of a normal male child weighing 7½ pounds. At the last writing in December, 1948, the baby is normal in every manner. Menses have continued normally since delivery.

In a patient with primary menstrual irregularities, long episodes of amenorrhea were interrupted by periods of spotting and occasional bleeding. The diagnosis of glandular-cystic hyperplasia was unequivocally established by repeated biopsy. Hormonal medication was helpful in the bleeding phase, but amenorrheic phases were not influenced. X-ray administered to the pituitary gland gave no clinical improvement. Normal menses, however, were established by x-ray therapy to the ovaries and two pregnancies followed. The first ended in abortion ten weeks after completion of radiation. The second pregnancy eleven months after radiation therapy was uneventful and resulted in the birth of a normal child. Menses have continued normally since confinement.

CASE 2.—Miss E. G., aged 24 years, was first seen Nov. 24, 1934, complaining of scant and irregular vaginal bleeding. The past medical and surgical history was irrelevant. Menses began at 13½ years, recurring regularly every 28 days for 5 to 6 days. For the past four years following a severe cold (nontuberculous) menses ceased, but occasional spotting appeared at irregular and widely separated intervals. There were three scant bleeding episodes in January, March, and April of 1934. The general physical examination was essentially negative. Pelvic examination showed hypoplastic external genitals, a small cervix and a congenitally retroverted hypoplastic uterus. The right ovary was slightly enlarged and cystic, the left ovary was normal. X-ray of sella turcica was normal. The blood count was normal. The basal metabolism rate was -17 per cent. The patient was placed on a high-protein diet with thyroid, ½ grain three times a day, after meals, gradually increasing the dose to 4 grains each day. Injections of estrogens (dose 15,000 I.U.) three times per week for two weeks, followed by chorionic gonadotropin 1,000 Units two to three times per week for two

Fig. 1 (Case 1).—Classical "Swiss cheese" hyperplasia. A compact cellular stroma supports glands of irregular size, shape, and contour. The large round forms are prominent. Specimens taken Jan. 9, 1940. Similar biopsy findings Feb. 28, and April 18, 1940. (×120.)

Fig. 2 (Case 1).—Fourth endometrial biopsy Jan. 21, 1944. Hyperplasia of the endometrium persists but the stroma is less compact. To the right the multiplying glands are clumped, producing a focus of adenomatoid overgrowth. A similar pattern was found in the fifth biopsy on Feb. 11, 1945. (×120.)

Fig. 3.

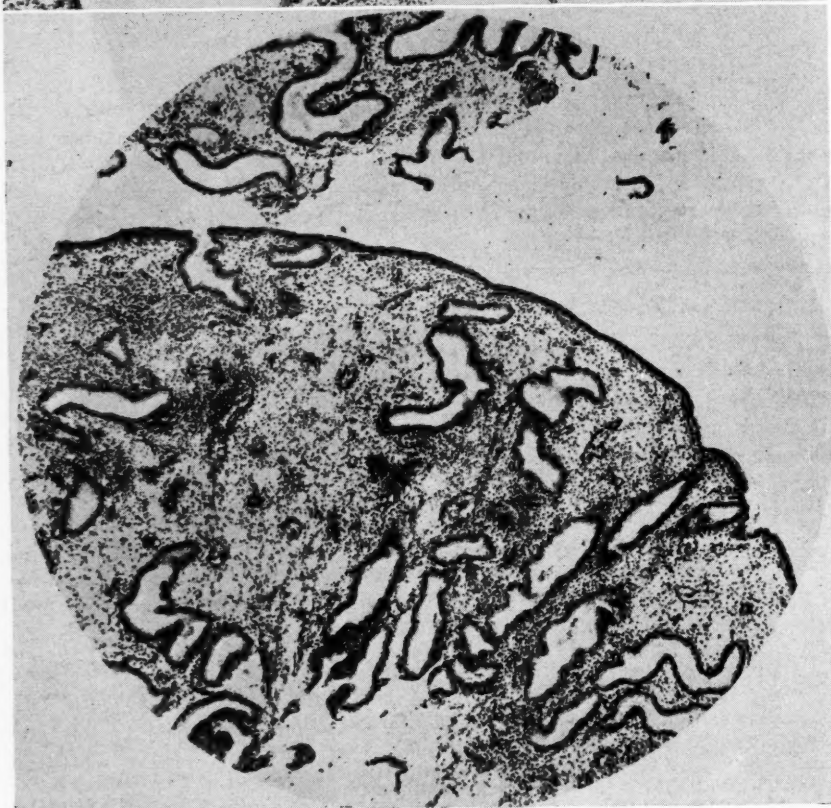
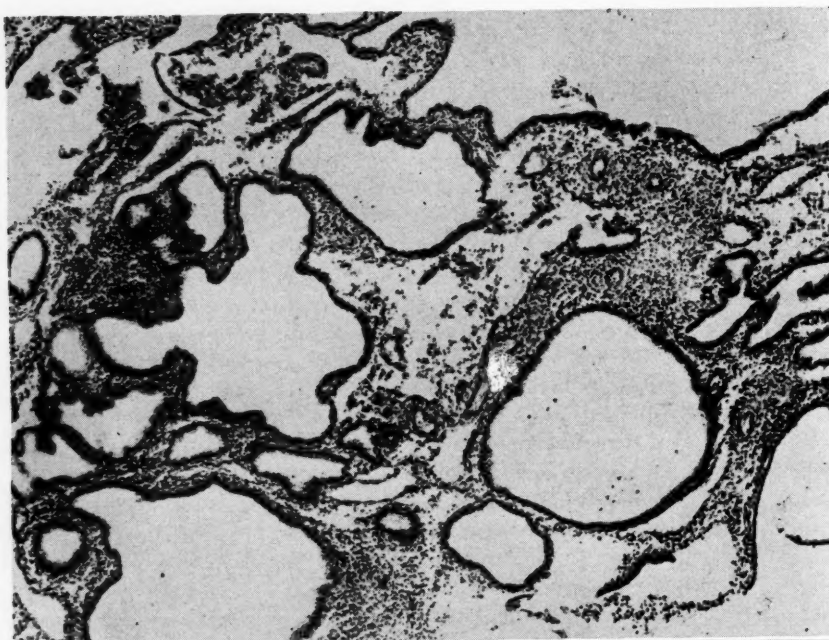


Fig. 4.

(See legends on opposite page.)

weeks were without result. The patient remained amenorrheic until May 21, 1935, when staining appeared. The physical findings were unchanged and the basal metabolic rate was now .8 per cent. There was no further bleeding in 1935. Staining and bleeding appeared irregularly after periods of amenorrhea varying from six to ten weeks throughout 1936, 1937, 1938, and 1939. Endometrial biopsy on Dec. 4, 1939, showed glandular-cystic and focal adenomatoid hyperplasia (Fig. 5). Gonadogen was now given intravenously in doses of 60 U. every second day for six doses and followed by injections of 10 mg. of progesterone every second day for six doses without result. Irregular spotting alternated with periods of amenorrhea as previously. The patient was married on Nov. 20, 1940. In April, 1941, the uterus was found to be normal in size and the ovaries were slightly enlarged. Thyroid extract was continued in daily doses 3 to 4 grains. Biopsy repeated Dec. 29, 1941, showed persisting glandular-cystic hyperplasia (Fig. 6). During February, 1942, a course of Synapoidin (10 c.c. in divided doses of 1 c.c. intramuscularly on alternate days) resulted in marked and cystic enlargement of both ovaries, and lower abdominal pain. All therapy except thyroid was then abandoned. On Feb. 23, 1934, the patient reported the symptoms unchanged and the pelvic findings were the same. X-ray therapy, although advised, was refused due to fear of permanent sterility and possible injury to subsequent offspring. Biopsy on Nov. 9, 1943, showed persisting hyperplasia. Similar findings obtained after a fourth biopsy on Feb. 16, 1944. Amenorrhea then persisted from Feb. 16, 1944, to Jan. 10, 1946, when irregular spotting returned. Occasional irregular and scant bleeding episodes returned and continued until Nov. 27, 1946, when a fifth biopsy again confirmed persisting hyperplasia. Between Jan. 4 and Jan. 25, 1947, x-ray to pituitary and ovaries was administered. Biopsy of the endometrium April 10, 1947, showed a premenstrual endometrium, and bleeding followed from April 17 to 22. During the remainder of 1947 menses recurred May 14 to 18, June 26 to 29, July 31 to August 3, September 14 to 19, October 31 to November 4, December 15 to 18 (a five-week cycle with regular flow). The patient was seen on Jan. 22, 1948, and the seventh biopsy showed a late premenstrual mucosa (Fig. 7). The ensuing menses followed Jan. 24 to 27, 1948. During the remainder of 1948 menses followed every six to eight weeks and were associated with fullness of the breasts and cramps in the abdomen.

Endometrial hyperplasia of thirteen years' duration was clinically manifested by protracted periods of amenorrhea, occasionally interrupted by episodes of scant staining. There was no response to glandular therapy. X-ray therapy to the pituitary gland and both ovaries was followed by restoration of a normal endometrial pattern, a secretory endometrium and a fairly regular five-week cycle. To date the use of contraception does not permit a statement as to the possibility of pregnancy.

CASE 3.—Mrs. S. R., aged 26 years, was examined Dec. 16, 1944, for complaints of oligomenorrhea, periods of amenorrhea, and sterility. The family and past personal history was negative. Menses began at 12½ years and continued irregularly every 2 to 3 months lasting 7 to 10 days. The last menses had occurred six months previously in July, 1944. The patient had been married for seven years and in spite of normal coitus in the past six years she had remained sterile. The husband was fertile. Physical examination revealed a patient of medium height and skeletal build, weight 123½ pounds. There were no bony abnormalities. The head organs were essentially negative. The thyroid was slightly enlarged. Heart and

Fig. 3 (Case 1).—Sixth endometrial biopsy. Endometrium June 19, 1945, ten weeks after completion of x-ray therapy to the pituitary. A mixed endometrial pattern is present. The glands are typically "Swiss cheese" type. The stroma cells about the spiral arterioles to the left, however, are enlarged, rounded, and lie in opposition. A compacta is thus present indicating antecedent ovulation. Menses, however, did not follow. ($\times 120$.)

Fig. 4 (Case 1).—Seventh endometrial biopsy on Aug. 23, 1946, eleven months after completion of x-ray to the ovaries. Pregnancy had occurred in November, 1945, after x-radiation, but terminated in miscarriage on Dec. 15, 1945. Menses in 1946 were regular and the last period had occurred July 30 to August 3. The endometrium shown above has been restored to normal. The stroma is edematous and comprised of small spindle cells. The glands are uniform, tortuous, and the lumina are wide and contain secretion. The lining cells show clarity of cytoplasm. The nuclei are uniform, oval, and are near the basement membrane. Menstruation followed August 30 to September 2. ($\times 80$.)

Fig. 5.

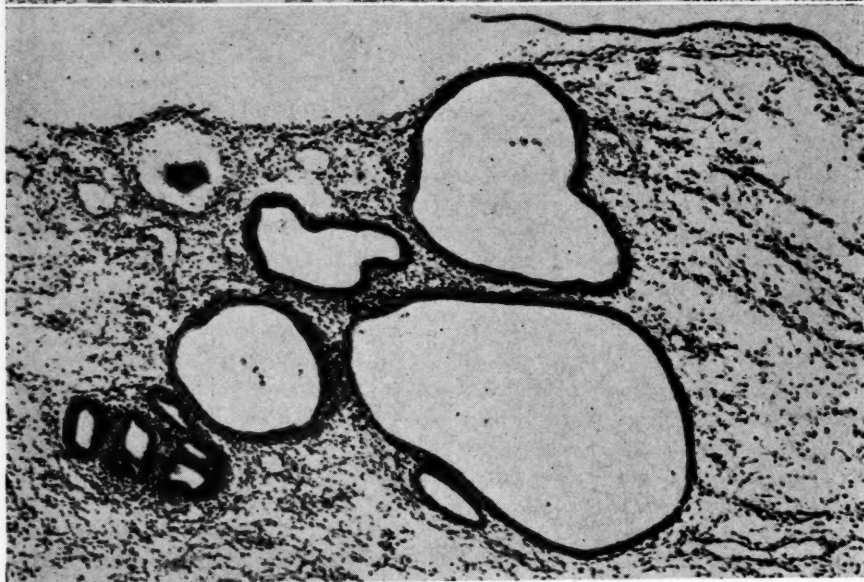
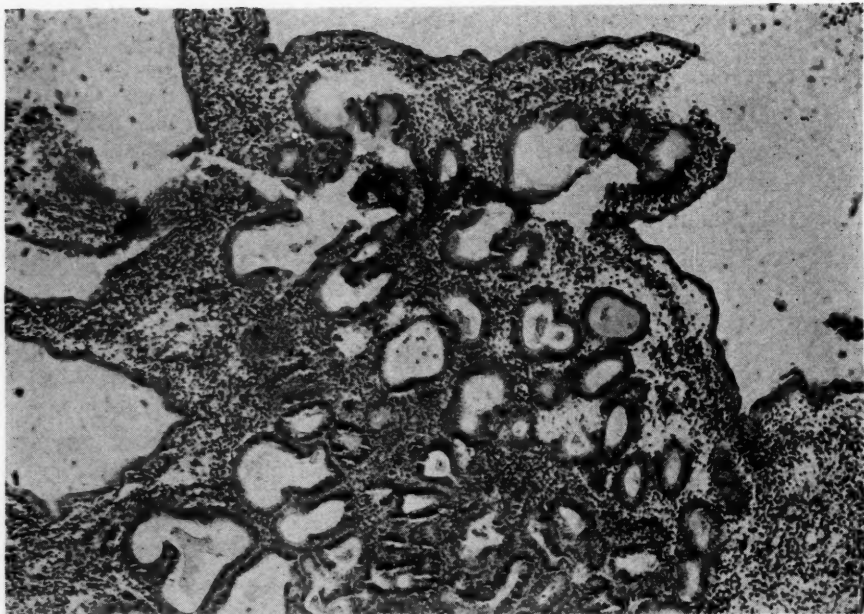


Fig. 6.

Fig. 5 (Case 2).—Endometrial biopsy Dec. 4, 1939, nine years after onset of prolonged periods of amenorrhea. To the left sections of large irregular glands surrounded by dense stroma. To the right is a focus of adenomatoid hyperplasia. The glands are of varied contour and closely set. The tall columnar cells possess large nuclei filling the cell body.

Fig. 6 (Case 2).—Second endometrial biopsy taken on Dec. 29, 1941. The large and irregular glands are closely set. To the left, the smaller glands are almost in opposition. The lining columnar cells show prominent large nuclei. The stroma, however, is atypical. Edema is marked and the cells generally elongated. A third biopsy on Nov. 4, 1943, showed essentially the same findings. No deviation was noted in the fourth biopsy Feb. 16, 1944, and the fifth biopsy Nov. 27, 1946. ($\times 120$.)

lungs were normal. The abdomen was hirsute but otherwise normal. The extremities were negative. Vaginal examination revealed normal external genitals. The cervix was short and the uterus small and retrocessed. The adnexa were not enlarged. A basal metabolism test on December 20 showed a value of -14 per cent. Endometrial biopsy on December 23 (Fig. 8) was reported as glandular-cystic hyperplasia. Vaginal smears showed follicular phase. Stilbestrol, 1 mg. 4 times per day, was begun on Jan. 9, 1945, and continued for ten days. Thyroid $\frac{1}{2}$ grain, three times a day, after meals, was also prescribed. Bleeding began January 25, and continued for twelve days until Feb. 6, 1945. This was "withdrawal bleeding," after stilbesterol, for a second biopsy on Feb. 2, 1945, showed persistent hyperplasia. Edema of the stroma was interpreted as an estrogen effect from stilbesterol. Amenorrhea, however, followed in spite of thyroid intake of 3 grains per day, and accordingly a course of Synapoidin (10 c.c. in divided doses of 1 c.c. intramuscularly on alternate days) was given between April 4 and April 24, 1945. Staining began on April 24, and continued intermittently.

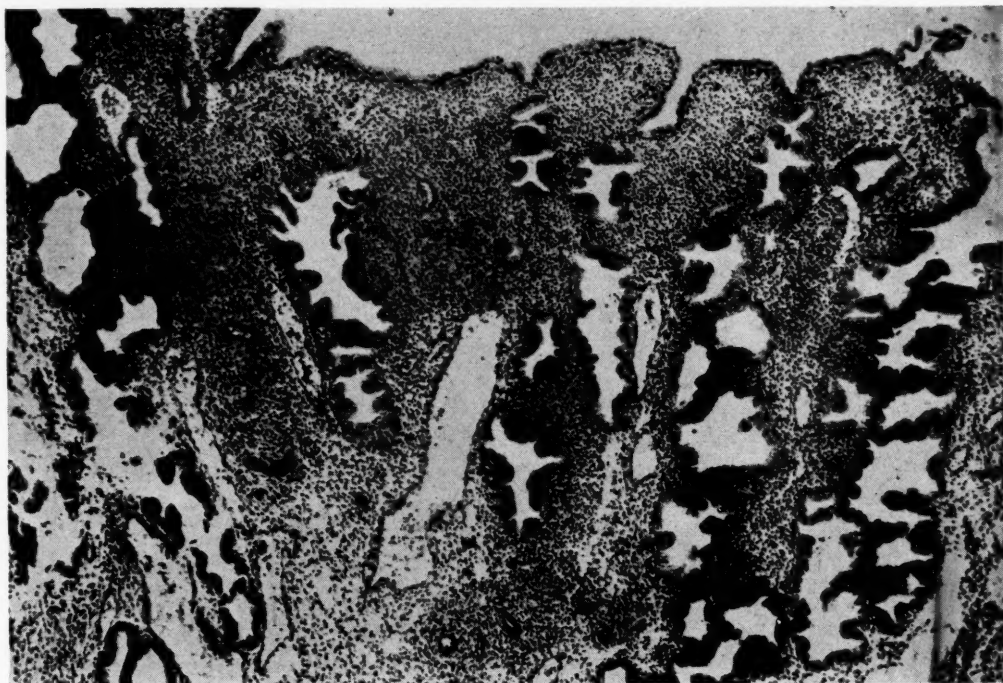


Fig. 7 (Case 2).—Seventh biopsy Jan. 22, 1948. Preceding menses Dec. 15 to 18, 1947. The endometrium is fully restored. A late premenstrual pattern is present. The compacta is well differentiated. The uterine glands are classically serrated. Secretion, however, is not prominent. ($\times 120$.)

The third biopsy on May 8 showed persisting glandular-cystic hyperplasia. Bleeding ceased on May 19. Examination on May 26 showed some enlargement of the uterus, both ovaries were palpable, but not abnormally enlarged. Staining returned May 28 and continued until June 7. Thyroid extract was continued in previous dosage. Staining again appeared June 26 and continued until July 1. The pelvic findings remained the same and a fourth biopsy on July 10 showed no deviation from the pattern of glandular-cystic hyperplasia. In spite of the use of extract thyroid and cyclic use of stilbesterol (1 mg. for 20 days followed by conjoined use of progesterol 10 mg. for 10 days), amenorrhea continued. The fifth biopsy on December 15 revealed persisting hyperplasia. On Feb. 7, 1946, the patient was referred for x-ray therapy to pituitary and ovaries. High voltage x-ray was employed by Dr. I. C. Kaplan with the following factors: 200 kv., 10 Ma., with 0.5 mm Al. as filter at 50 cm. target distance. Treatment was directed through anterior and posterior right and left pelvic fields

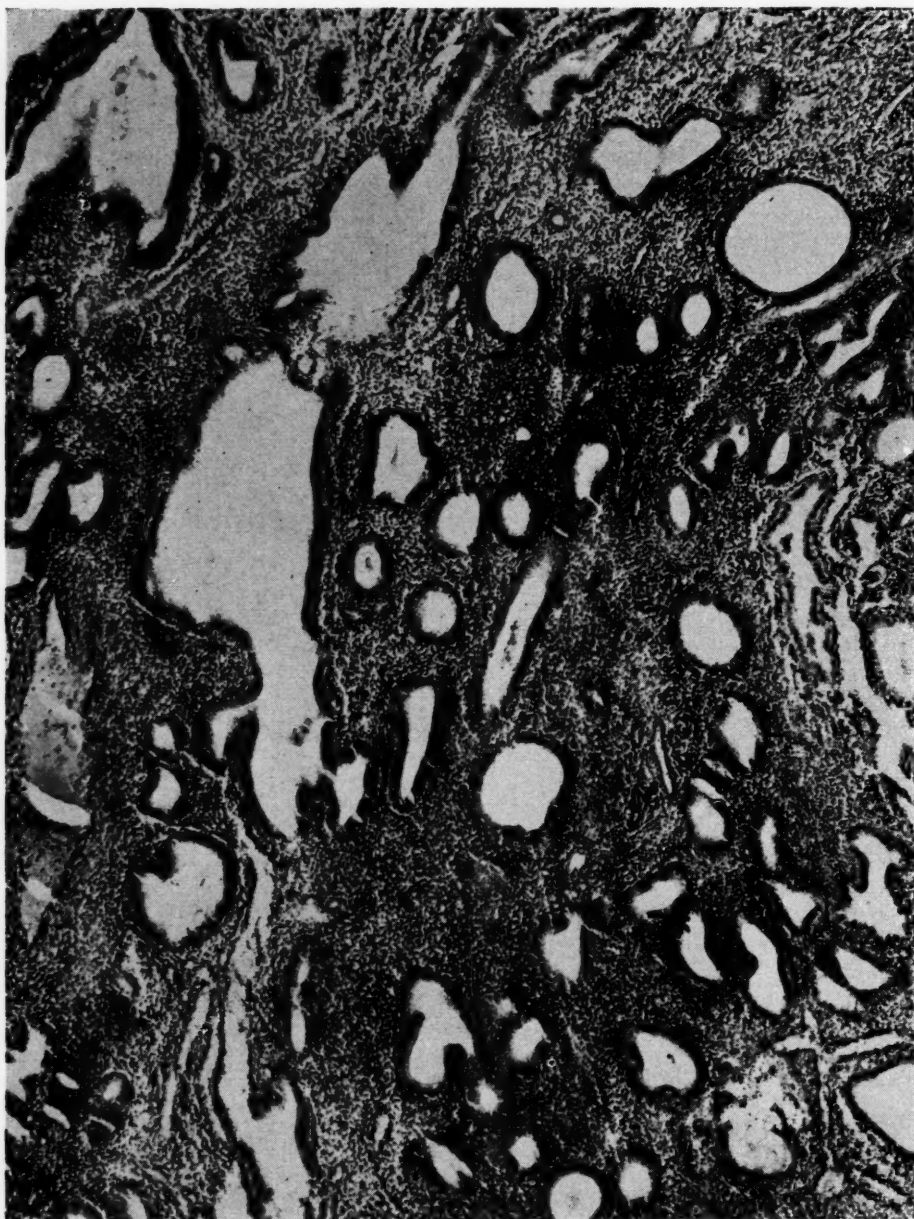


Fig. 8 (Case 3).—First endometrial biopsy Dec. 23, 1944. Classical endometrial hyperplasia. A dense compact stroma of large, round cells supports large numbers of endometrial glands of varied size and contour. The large irregular types are characteristic. A similar pattern was found on second biopsy Feb. 6, 1945, and also on biopsies May 8, July 10, and Dec. 15, 1945. ($\times 120$.)

Fig. 9 (Case 3).—Sixth endometrial biopsy taken April 4, 1946. X-ray therapy to pituitary and ovaries completed March 5, 1946. The persisting hypertrophied glands lie in a loose stroma. The cells are low to medium columnar. To the right are small glands of fairly uniform contour. The lining cells are tall and contain clear cytoplasm. Basal secretion has caused recession of the nuclei from the basement membrane toward the inner cell border resulting in a well-marked zona pellucida. This is indicative of recent ovulation. Menses followed April 13 to 16, 1946. ($\times 120$.)

Fig. 10 (Case 3).—Seventh endometrial biopsy May 9, 1946, on the twenty-sixth day of the cycle. Hyperplasia has disappeared. The superficial stroma is edematous. The glands are slightly tortuous. The nuclei are tall and fill the cell body. They are almost uniformly aligned. Ovulation is delayed. Menses followed May 24 to 28. Cycles continued regularly every five weeks until pregnancy occurred in August, 1946, five months after completion of x-ray therapy. Unfortunately, this pregnancy terminated in a complete spontaneous abortion at 14 weeks. ($\times 120$.)

Fig. 9.

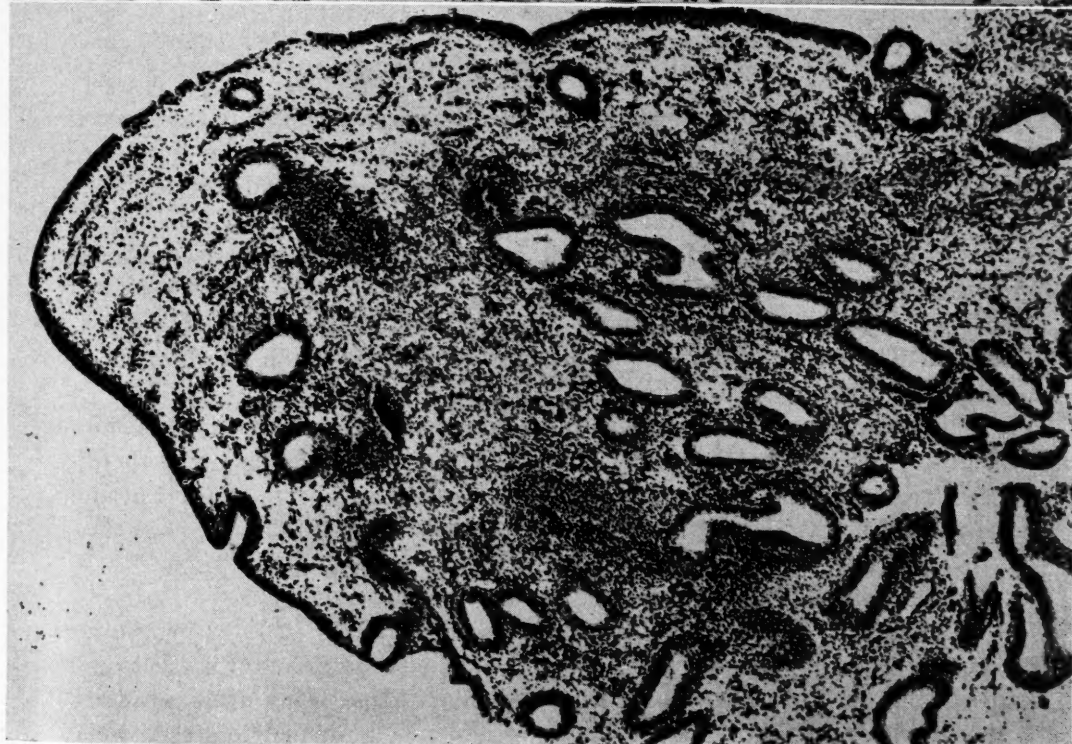
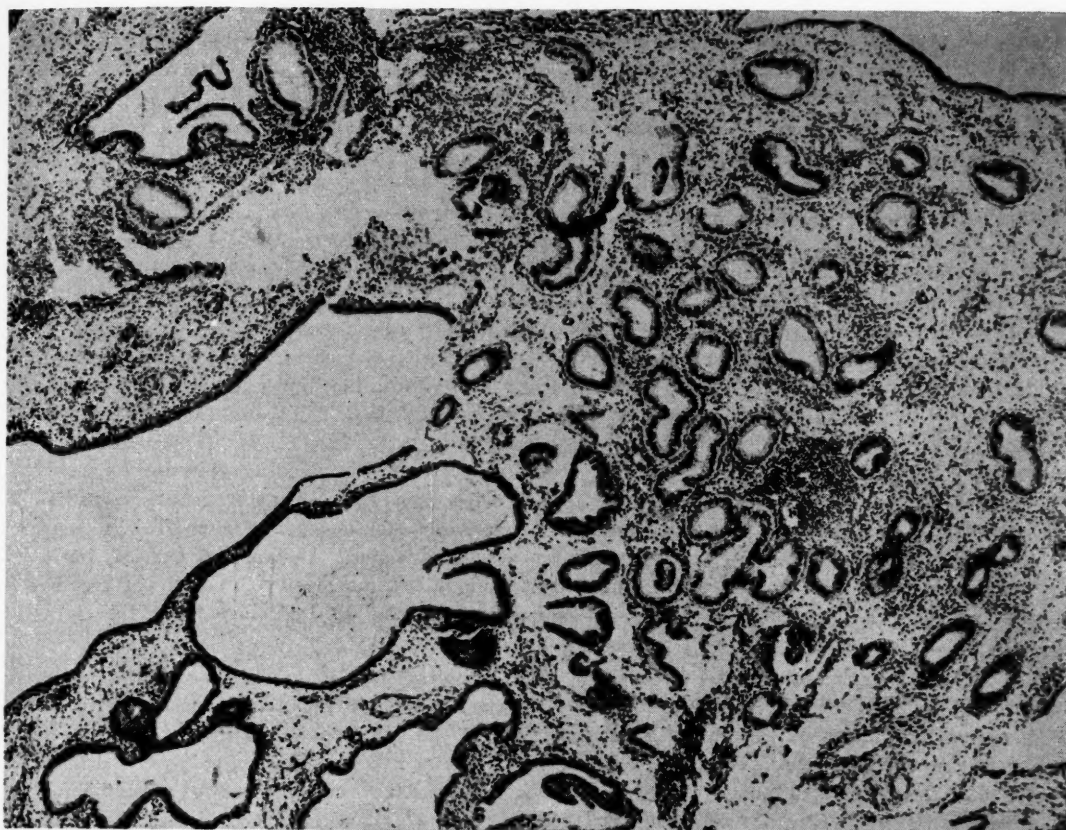


Fig. 10.

(See legends on opposite page.)

through an 8 by 10 cm. portal. The pituitary was treated through a 6 by 8 cm. field, the dose was 50 to 75 r. (measured in air) per treatment at weekly intervals for three weeks. The pelvis was irradiated anteriorly the first week and posteriorly the second week and again anteriorly the third week, also using 50 to 75 r. (measured in air) per treatment at weekly intervals for three weeks. The above was completed on March 5. A sixth biopsy on April 4, showed regressive cystic hyperplasia, with focal zones of returning function, for many glands showed a clear-cut zona pellucida, typical of post ovulation (Fig. 9). Bleeding followed from April 13 to 18, 1946. The uterus was now larger in size, the ovaries were not felt. The seventh biopsy (Fig. 10) on May 9 showed a postovulatory endometrium and a normal period occurred May 24 to 28. Other menses occurred July 5 to 9 and August 6 to 10. When seen Oct. 8, 1946, after two months of amenorrhea, the uterus was noted as enlarged and soft. A diagnosis of pregnancy was confirmed by a positive Aschheim-Zondek test on Oct. 14, 1946. Notwithstanding the use of thyroid and Progesterol, bleeding and cramps appeared November 18, and a complete spontaneous abortion occurred Nov. 21, 1946. Menses returned January 2 to 6, 1947. A repeat basal metabolism test on January 8 was -17 per cent and thyroid, 1 grain three times a day, was accordingly resumed. Bleeding episodes occurred February 13 to 18 and March 13 to 18, 1947. When seen June 17, after twelve weeks of amenorrhea, the uterus was enlarged and soft. An Aschheim-Zondek test June 18 was positive for pregnancy. The antepartum course was without incident. Delivery on Dec. 21, 1947, was accomplished by low forceps for outlet dystocia due to funnel pelvis. The living female child, normal in every manner, weighed 6 pounds, 12 ounces. In December, 1948, the child is physically and mentally normal for a child 1 year of age.

Persisting glandular-cystic hyperplasia was associated with long periods of amenorrhea followed by episodes of bleeding. The course was not influenced by varied types of hormone therapy. Involution of the abnormal endometrium to the functional type by x-ray is shown in the microphotographs. The first pregnancy, five months after completion of x-ray therapy, ended in complete spontaneous abortion. A second pregnancy one year after radiation resulted in the birth of a normal living girl. Since delivery, menses have continued regularly every five weeks.

Conclusions

1. Glandular-cystic hyperplasia of the uterine endometrium is often the cause of prolonged periods of amenorrhea mingled with irregular episodes of staining or bleeding. Diagnosis is absolutely established by endometrial biopsy. Exclusion of other lesions is indicated above.
2. Return of a normal endometrial pattern or normal menstrual function by hormone therapy is often unsuccessful.
3. In such resistant cases, x-ray therapy to the pituitary and ovaries is indicated. Ovulation recurs, menstrual bleeding proceeds from a secretory endometrium, and fertility is established.
4. Restoration of endometrium to normal pattern is shown by the microphotographs of endometrial tissue studied before and after radiation therapy.
5. Pregnancy soon after x-ray therapy results in abortion, for the endometrium may not have been fully restored to function.
6. Later pregnancies proceed to term without incident.
7. The babies at birth and in early infancy are normal.
8. Anomalies in immediate offspring, as also defects in later generations, are possibilities in light of genetic experiments. To date, however, there is no evidence that such changes have occurred in the human being after x-radiation to the ovaries. In this light pregnancy should not be denied to sterile women who have exhausted all other therapeutic means.

References

1. Brewer, J. I., and Jones, H. O.: AM. J. OBST. & GYNEC. 55: 18, 1948.
2. Drips, D. G.: AM. J. OBST. & GYNEC. 55: 789, 1948.
3. Edeiken, Louis: AM. J. OBST. & GYNEC. 25: 511, 1933.
4. Hirsch, I. S.: Radiology 7: 93, 1926.
5. Hoffman, J.: Female Endocrinology, Philadelphia, 1944, W. B. Saunders Company, p. 323.
6. Kaplan, Ira I.: AM. J. OBST. & GYNEC. 21: 82, 1931; AM. J. OBST. & GYNEC. 23: 426, 1932; J. A. M. A. 121: 1199, 1943; New York State J. Med. 48: 2746, 1946.
7. McKelvey, J. L., and Samuels, L. T.: AM. J. OBST. & GYNEC. 53: 627, 1947.
8. Muller, Herman J.: In O. Glasser, editor: The Science of Radiology, Springfield, Ill., 1933, Charles C Thomas.
9. Rubin, I. C.: AM J. OBST. & GYNEC. 12: 76, 1926.

1530 PRESIDENT STREET
BROOKLYN, NEW YORK

Tyler, Edward T.: Use and Misuse of Endocrine Therapy in Sterility, J. A. M. A. 139: 560, 1949.

The author found that endocrine causes constitute only 20 to 25 per cent of involuntary sterility. Probably one of the most frequently treated functional disorders in infertility is a failure of ovulation. Endocrine therapy of anovulation has not been successful. Preparations containing large amounts of follicle-stimulating hormone are most valuable. The use of preparations containing pregnant mare's serum has been disappointing to the author. A hypoplastic uterus is frequently a feature in a generalized state of hypogonadism. Development of the hypoplastic uterus can be induced by estrogenic therapy and dosage should be heavy. Poor corpus luteum function may be another factor. The treatment of habitual abortion with endocrines has also been disappointing, indicating a lack of knowledge of the etiology of this condition. From the scientific point of view, thyroid should be given only in cases of hypothyroidism which is based on the basal metabolic rate, blood cholesterol, and blood iodine. There is a definite question as to the value of its routine usage.

In the male the two major conditions in which hormones may be involved are (1) impotence, and (2) defective spermatogenesis. In impotence testosterone propionate may be of some value. Neurogenic and psychogenic factors may be of some importance. Hormonal stimulation of sperm production is not encouraging. In cases where the sperm count is fairly normal but motility is impaired small doses of testosterone may be of some benefit. Thyroid should be used in cases of hypothyroidism.

WILLIAM BERMAN.

THE TREATMENT OF EARLY CARCINOMA OF THE CERVIX UTERI*

JAMES A. CORSCADEN, M.D., NEW YORK, N. Y.

*(From the Sloane Hospital for Women and the Department of Obstetrics and Gynecology,
College of Physicians and Surgeons, Columbia University)*

THE treatment of carcinoma of the cervix a decade ago was fairly well stabilized with the general abandonment of nearly all techniques, operative and radiologic, in favor of intracavity radium combined with external x-ray. Today, with the revival of the radical operation and of the transvaginal application of x-ray, and improvement in the interstitial use of radium together with a new problem posed by the most frequent discovery of intraepithelial carcinoma, the therapy of cancer of the cervix must again be reviewed and an evaluation of the various procedures made.

The definition of early carcinoma of the cervix as here used implies that the cancer is limited to the cervix and is one in which there is a completely free choice of treatment, operative, radiologic, or other. In the Sloane Clinic we have employed the League of Nations Classification but found that with Stage I there were lesions of such varying extent that they constituted significantly different stages, and therefore subdivided it. Since 1929 we have included in Stage Ia all of those cases which were not visible or palpable, including cases which were frankly invasive, three cases of intraepithelial carcinoma and one case in which the diagnosis was disputed but which received treatment for carcinoma. Stage Ib corresponds to Schmitz I and indicates those clinically appreciable lesions which are smaller than one centimeter in diameter. Stage Ic includes all of those still limited to the cervix and above one centimeter in size.

In the future, we propose to employ still another classification, one in which the intraepithelial lesion is given a separate value. Since in the intensive study which is now being made of intraepithelial cancer, there is doubt on the part of many as to whether this should be called a true cancer or a condition which would better be called precancerous, we propose to label these lesions "o" and classify the invasive lesions as Ia, b, c, II, III, IV.

In the active treatment of cancer of the cervix, historically all of the methods available today are of fairly ancient origin. (Hysterectomy, 1878,² radical hysterectomy, 1895,³ x-ray therapy, 1896, transvaginal x-ray, 1901,⁴ and radium, 1903.⁵ It would appear that we have little new to offer in the way of therapy. What have changed, however, are the details through which the principles have been carried out, particularly the care of the patient undergoing an operation and, in radiation, greater knowledge of and precision in the application of a "tumor dose."

One or more of these methods will be applied to three different situations: in the first there are numerous positive Papanicolaou smears and yet no car-

*Presented, by invitation, at a meeting of the Philadelphia Obstetrical Society, Dec. 2, 1948.

cinoma discovered by biopsy. In this the treatment depends upon balancing the reliability of the report of the smear against the needs of the woman. If the examiner of the smear rates at the top and the patient is a good operative risk, desires no more children, and is one to whom an artificial menopause would be acceptable, this situation may be handled as is the intraepithelial cancer. If destructive therapy is to be avoided, she may be observed monthly but will always be suspected of having a cancer.

Intraepithelial carcinoma of the cervix has been cured by the taking of a biopsy, by excision with the high frequency current, by amputation of the cervix, simple complete hysterectomy, and intracavity radium. Whether one applies a simple or more radical procedure depends on his concept of what the disease is. Until more information is available, we will state dogmatically that in women to whom the menopause is objectionable, we will perform a wide complete hysterectomy and in those to whom the menopause is welcome, will employ a full cancer dose of intracavity radium. The five-year cure following either treatment has been 100 per cent.

The evaluation of the treatment of frank invasive cancer of the cervix will be made on the basis of the conventional five-year postoperative survival. While the ten-year results may show significant differences, the difficulties of selection presented by deaths from intercurrent disease make this interval too long for a practical judgment. The three-year interval has been suggested with the idea that the five-year result, by interpolation, might be predicted. This has been found unsatisfactory.⁶ Our immediate objective is to find that therapy which, if applied today to an early carcinoma, would give the best prognosis. For that purpose we shall study the results of the various techniques in those cases which have been treated most recently rather than in those treated many years ago.

Taking up first intracavity radium combined with external x-ray, this has been the method employed in the treatment of cancer of the cervix at Sloane Hospital in all of the cases here reported. Table I is a summary of the results from 1917 to 1943. The apparent improvement in the results is in part real and in part due to improvement in follow-up since we have followed the statistically imperfect convention of classifying all cases not followed as dead of cancer. From 1917 to 1929 the cases were treated in two hospitals, with unsystematic techniques and without adequate follow-up. With the establishment of the Medical Center, a Sloane Hospital Neoplasm Clinic was formed in the outpatient department (1929). This presentation is from a general gynecologic service in which this special group interested in neoplasms aided the members of the staff, some twenty in number, in planning and executing the therapy for cancer of the cervix.

The technique employed in the application of intracavity radium from 1929 to 1937 was to insert 100 mg. of radium in a tandem in the cervical and uterine canal. In each lateral fornix and against the cervix was placed a 25 mg. tube of radium making the total application 175 mg. which was left in place for forty hours, giving a total of 7,000 mg. hr. Because of intestinal injuries caused by rapid, intensive irradiation both by radium and x-ray,⁷ we, in 1937, changed the radium installation to one in which 30 to 40 mg. of radium were placed in tandem in the cervix and corpus, a 10 mg. tube of radium was placed in each

TABLE I. CARCINOMA OF CERVIX. FIVE-YEAR RESULTS FOLLOWING INTRACAVITY RADIUM
COMBINED WITH EXTERNAL X-RAY

STAGE LEAGUE OF NATIONS	1917-1928			1929-1933			1934-1938			1939-1943		
	NO. CASES	PER CENT WELL	PER CENT WELL	NO. CASES	PER CENT WELL	PER CENT WELL	NO. CASES	PER CENT WELL	PER CENT WELL	NO. CASES	PER CENT WELL	PER CENT WELL
I	?	?	?	31	43.	64.	45	64.	51	76.		
Absolute	181	10.	50.	137	19.	36.	157	36.	149	43.		
Not followed	93	50.		31	23.	6.	8	6.	7	4.		

TABLE II. FIVE-YEAR RESULTS IN 443 CASES OF CARCINOMA OF CERVIX TREATED BY INTRACAVITY RADIUM COMBINED WITH EXTERNAL X-RAY

STAGE LEAGUE OF NATIONS	1929-1933					1934-1938					1939-1943				
	NO. CASES	NO. WELL	PER CENT	NOT FOL.	PER CENT	NO. CASES	NO. WELL	PER CENT	NOT FOL.	PER CENT	NO. CASES	NO. WELL	PER CENT	NOT FOL.	PER CENT
Ia	1	1	100	-	-	2	2	100	-	-	6	6	100	-	-
Ib	5	4	80	-	-	13	10	77	-	-	8	7	88	-	-
Ic	25	8	32	5	20	30	17	57	-	-	37	26	70	2	5
I all	31	13	43	5	16	45	29	64	-	-	51	39	76	2	4
II	31	5	16	5	16	47	18	38	5	10	44	17	40	3	7
III	61	6	10	16	26	48	5	10	-	-	28	1	4	-	-
IV	5	0	-	1	20	4	1	25	-	-	6	0	-	-	-
Stump	2	1	50	-	-	6	3	50	2	33	20	7	35	2	10
Unclassified	7	1	14	4	57	7	1	14	1	14	-	-	-	-	-
Absolute	137	26	19	31	23	157	57	36	8	6	149	64	43	7	4

lateral fornix, and one against the cervix. The filtration was 1 mm. platinum with secondary 5 mm. of gauze in the vaginal plugs. These were left in place one hundred hours. A 60 mg. application (6,000 mg. hr.) gave in the external os a dose of 18,000 gamma roentgens, in the paracervical region 11,580 gamma roentgens, and in the lateral pelvis, 1,500 gamma roentgens. X-ray through two anterior and two posterior ports, 10 by 15 cm. beamed laterally—200 kv., 1 mm. cu. and 1 mm. pt. filter, 50 cm. anode skin distance—200 r. to 400 r. daily dose to a total of 2,000 r. measured in air to each port gives additional radiation of 3,886 r. in the cervical mass, 3,886 r. in the paracervical region, and 2,546 r. in the lateral pelvic region.

By this technique there was delivered to the cervix and immediate paracervical region an adequate cancerocidal dose and in the lateral pelvis one that was inadequate.

The dose outlined is obtained when the radium can be inserted as indicated. In some cases distortion of the vagina or cervix makes this impossible. We find in consequence that of the 149 cases treated in 1939 to 1943, 41, or 26.2 per cent, received inadequate radium. Likewise x-ray occasionally was limited by illness or lack of cooperation of the patient, rarely by the therapist, so that 19, or 12.8 per cent, received inadequate x-ray therapy.

Table II is a more detailed analysis. Stage I is broken down into the before-mentioned subclasses. Considering the cases treated in 1939 to 1943, all of the subclinical cancers were cured. Stage Ib represents the earliest cancer which could be diagnosed without special techniques and is perhaps the stage of carcinoma which should be the object of our most intensive attack. Of the eight cases in this group, seven, or 88 per cent, survived five years. All cases were followed. In the large lesions still limited to the cervix (Stage Ic), of 37 patients treated, 26, or 70 per cent, have survived five years. Two cases were not followed. Two patients died of intercurrent disease, one of splenohepatomegalia which antedated a Stage Ib carcinoma and one of cerebral thrombosis four years after irradiation for a Stage Ic carcinoma.

In summary, our results, 76 per cent (83 per cent relative) for Stage I, League of Nations, and 43 per cent absolute (46 per cent relative), were achieved during the years 1939 to 1943 in 149 cases of which 51 were Stage I. (Two cases of Stage I and seven cases in all were not followed.)

The number of cases (149) is too small for statistical validity. We therefore have compared our results with those obtained in recent years in other places. Heyman gives the results obtained at the Radiumhemmet from 1915 to 1941 in 4,611 cases followed five years (Fig. 1).⁸ The five-year cures rose from about 50 per cent in Stage I League of Nations to 72 per cent and from an absolute cure rate of 20 per cent to one of 40 per cent.

Table III is a compilation of reports of treatment rendered in recent years in clinics situated in various parts of the world. As in most compilations of this sort, these numbers should not be compared literally one with the other because of the large degree of selection. Heyman's "absolute" is strictly according to the League of Nations Classification. Miller and we exclude cases not treated by us. Hynes⁹ classes as "indeterminate" cases partially treated elsewhere, recurrent growths, and others, and excludes them in the worthy desire to present the "results of a particular method of treatment." Likewise, the classification of the growth into various stages must not be taken too literally. Some exclude and others include intraepithelial cancer in Stage I. The delimitation between Stages I and II is determined by palpation and is obviously very broad. Also, allowance must be made for the type of treatment given. In Kimbrough's report, the absolute cure rate was 27.6 per cent but in cases receiving "adequate" treatment, the cure rate was 38.8 per cent.¹⁰

TABLE III. COMPILATION OF FIVE-YEAR RESULTS OF COMBINED INTRACAVITY RADIUM AND EXTERNAL X-RAY OBTAINED IN VARIOUS CLINICS

AUTHOR	SOURCE	YEARS	TOTAL	STAGE I		CURES IN PER CENT	
			CASES	CASES	PER CENT	STAGE I	ABSOLUTE
Heyman ⁸	Stockholm	1934-38	1,224	102	8	67	37
Hurdon ³¹	London	1934-37	807	40	5	80	36
Paterson and Tod ³²	Manchester Manchester	1932-39	771	23 35	8	62 (a) 76 (b)	29
Schmitz ³³	Chicago	1933-42	166	48	29	77	43 (c.f.)
Miller ³⁴	Michigan	1939-42	435	59	14	68 (c)	43.7
Bowing ³⁵	Mayo Clinic	1935-39	300	—	—	—	48.5 (d)
Richards ³⁶	Toronto	1929-40	862	92	10	74	36
Kimbrough ¹⁰	Pennsylvania	1933-41	130	45	35	53 (e)	28
Hynes ⁹	Delaware	1935-42	156	76	50	71 (e)	51 (e)
Karr ³⁷	Rochester, N. Y.	1938-42	120	35	29	74	38
Baud ³⁸	Paris	1929-41	105	105	—	70	— (b)
Munnell and Brunschwig ¹¹	Memorial Hospital, N. Y.	1934-41	1,037	200	20	53	29
This study	Sloane Hospital, N. Y.	1939-43	149	51	34	76	43

(a) Treated by intracavity radium and external x-ray.

(b) Treated by intracavity radium alone.

(c) Results reduced to agree with League of Nations Classification.

(d) Exclusive of cases not traced.

(e) Including only cases treated according to a plan.

(f) 800 kv. external x-ray.

It will be seen, however, that there has been in the later years a generally reported salvage of about 70 per cent or better in Stage I and an absolute cure rate of about 40 per cent or over in every part of the world where the intracavity method has been employed. An important exception to this is the report by Munnell and Brunschwig¹¹ in which, between 1934 and 1941 in 1,037 cases of which 200 were Stage I, the five-year salvage rate for Stage I was 53 per cent and the absolute rate 29 per cent. Despite this exception, we believe that it is fair to say that a minimum of 70 per cent five-year survival in Stage I and 40 per cent in all cases diagnosed as cancer should be the accepted minimum standard in cases treated by intracavity radium combined with x-ray.

Taking up now the operative treatment of carcinoma of the cervix, we shall divide it into two parts, first the Wertheim operation as performed up to the time when it was so generally abandoned, and second, the operation as it has been recently revived. We can save time in discussing the first part by presenting a quotation from Fletcher Shaw¹² of the Manchester Clinic in 1937 which in scholarly fashion gives the reason why this clinic, noted for its superior surgery, had abandoned the operation in favor of the intracavity use of radium combined with external x-ray.

"After careful observation of these cases for over seven years, Prof. Dougal and I have come to the definite conclusion that radium offers the best chance of cure as well as being the more humane method of treatment. Therefore, strong advocates though we were of operation, we have now abandoned it."

This capitulation was indeed late. Most of the clinics which had radium available had abandoned the operation ten or more years previously.

An evaluation of the revived Wertheim operation is more difficult. Results upon which we are to base our evaluation are scant. Read carrying on in the Chelsea Hospital, London, following in the footsteps of Bonney, Morton following Lynch in San Francisco, and Masson for the Mayo Clinic represent a carry-over from the old to the new.

Read¹³ (Table IV) in 34 cases Stage I, operated upon between 1936 and 1941, constituting 14 per cent of all cases examined, reports a five-year salvage of 41 per cent and, in Stage II, 20 cases with a five-year salvage of 50 per cent.

Morton¹⁴ in 88 cases, constituting 10 per cent of all cases examined, reports a five-year salvage of 64.7 per cent.

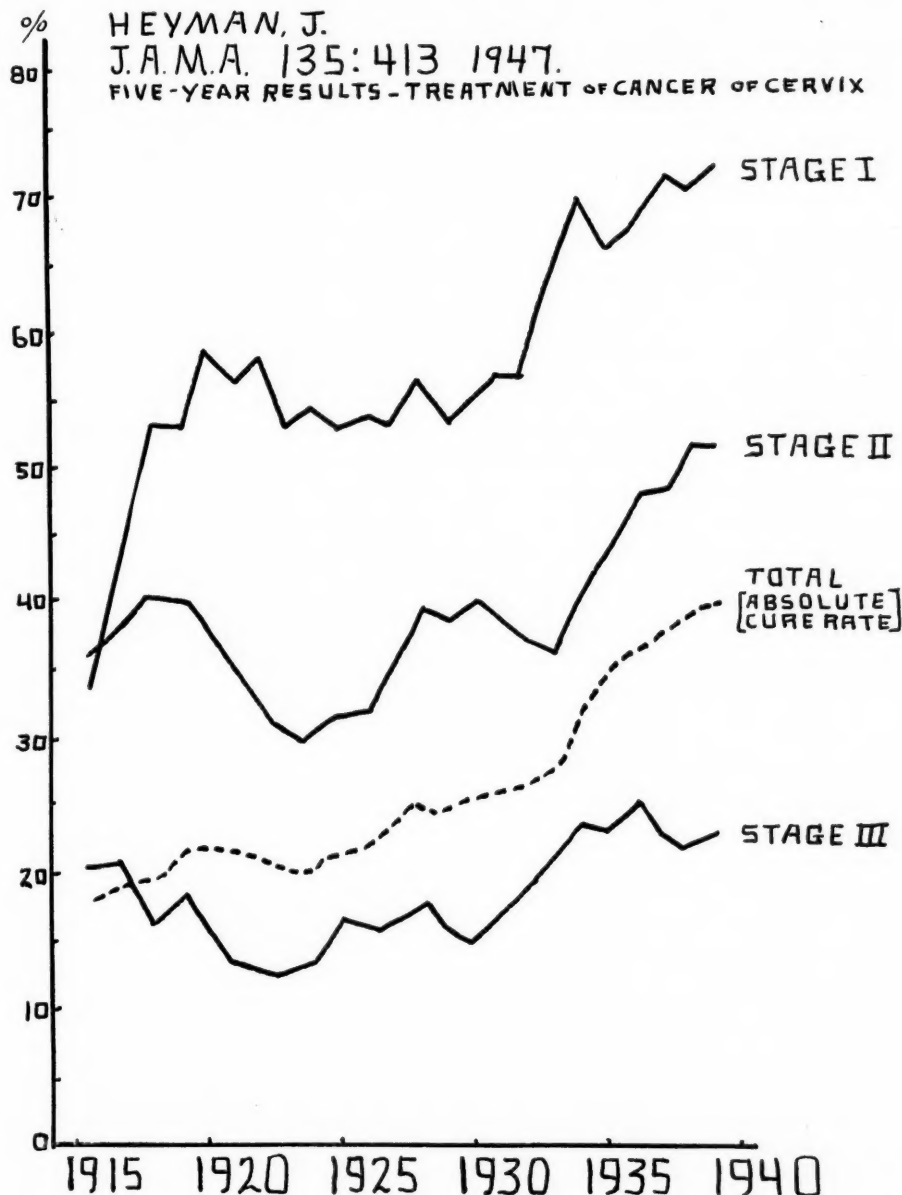


Fig. 1.

Masson¹⁵ reports 81 cases treated by the Wertheim hysterectomy constituting 8.8 per cent of all cases. Eighteen of these were true Wertheim operations with a survival rate of 39.9 per cent. Sixty-three cases treated by operation combined with irradiation had a survival rate of 73 per cent.

Meigs,¹⁶ taking up the operation anew, in 36 cases, constituting 10 per cent of all cases treated, reports a three-year salvage of 77 per cent. Of seven patients having metastases in the lymph nodes, two, or 27 per cent, survived.

TABLE IV. RESULTS FOLLOWING "REVIVED" WERTHEIM HYSTERECTOMY

AUTHOR	SOURCE	YEARS	NO. CASES	PER CENT OF TOTAL	5-YEAR CURE PER CENT
Read	London League of Nations	1936-41	34	14	41
		1936-41	20		50
Morton	San Francisco	---- 40	88	10	64.7
Masson	Mayo Clinic	1930-40	18	8.8	38.9*
					3-YEAR CURE PER CENT
Meigs	Boston	---- 44	36	10	77

*63 additional cases treated by Wertheim hysterectomy combined with radiation: five-year survival 72 per cent.

Here again, even in these small groups, the numbers must not be taken literally. On the one hand a number of the cases operated upon had had previous radiotherapy and in some no cancer was found at operation; on the other, Dr. Masson, in discussing the operative treatment of cancer of the cervix, found that a large number had had an incomplete operation.

These results are obviously too scant to form a base upon which to make a decision but, as they stand, are definitely no better than, and in general slightly inferior to, those obtained from the intracavity use of radium combined with external x-ray. Another factor to be included in the evaluation is the type of case selected for treatment. The cases selected for operation constituted 10 to 15 per cent of the total cases with cancer of the cervix. Of the cases treated by radium, those classed as League of Nations I and by definition technically operable, constituted in our series 27 per cent of all the cases, and in the series compiled in Table III as many as 50 per cent of all cases. There is obviously a marked degree of selection. The proportion of survivors in the narrowly selected group should be higher than in the larger group.

Köhler and Haenisch¹⁷ by cooperative effort between a surgeon and a radiologist report from the Hamburg Clinic, between 1927 and 1938, 582 cancers of the cervix of which 315, that is 54.1 per cent, were treated by operation. Two hundred seventy-five were treated by the Bumm-Wertheim hysterectomy, followed by intensive roentgen treatment with a five-year survival of 183, or 67 per cent. The remainder of the cases were treated by intracavity radium and x-ray. The absolute cure rate of the 582 cases was 42.6 per cent. Reports of systematic irradiation in connection with the operation are rare. The results as published certainly are excellent.

Since the operation today, because of improved care of the operative patient, can be performed so much more safely and also more thoroughly, it is important that it be performed until enough experience has been obtained to form the basis for a proper judgment of this procedure. Also, when techniques are available for determining those cancers which are resistant to radiation, the operation will be performed in these cases without the application of any radiation. Third, a combination of radiation and operation may be worked out which will be more efficient than either alone. For these purposes it is important that this extensive procedure be carried out by exceptionally trained surgeons, with exceptional operative facilities. As many as twenty transfusions have been required. Unless the operation is so thorough as to need these facilities, it will be no more complete than it was when it was so generally abandoned.

The great harm caused by the recent emphasis on this radical operation is that many take it to be a new procedure although it is the oldest (1895) form of treatment, and others accept it as the established practice, in spite of the fact that some articles stress that the operation has only been revived in the hope that with the better care of the patient, and less need for haste, the operation may be more carefully and thoroughly performed than it was by Clark, Bonney, Wertheim, and the other masters. Moreover, the laity, their imaginations touched by the idea of "having it all out," are putting pressure on the surgeons to "operate." The results of this movement are already appearing in our City Cancer Hospitals. Patients are being admitted with persistent cancers, victims of incomplete surgery.

Lymphadenectomy following irradiation of the cervix with radium or x-rays as practiced by Taussig,¹⁸ Morton,¹⁴ Nathanson,¹⁹ and others must be classified as experimental until more results are available.

Transvaginal x-ray, first used in 1901, was revived in 1936 by Merritt and has been carried on by Caulk,²⁰ del Regato,²¹ Wasson,²² Erskine,²³ Pendergrass, and others. Two techniques have been devised. One in which the rays are directed through an unshielded cone to a single large field, the other in which through a cone shielded to the tip, the rays are directed to multiple small fields on the cervix and the fornices. Here again evaluation is made difficult by the scantiness of the published results. Most of the papers deal with techniques and dosage. Here are two reports of results following the use of the large single field.

Del Regato²¹ (Table V) reports 76 cases with a three-year absolute cure of 44 per cent and in ten cases with Stage I carcinoma a three-year cure rate of 60 per cent.

Caulk²⁰ reports a five-year cure of 44 per cent in 202 cases treated by the single-exposure technique alone or in combination with other forms of radiation. Seventy-two cases with Stage I had a five-year cure rate of 66 per cent.

The results of treatment by the multiple-field technique are expressed in a single contribution by Twombly²⁴ who reports 113 cases with a three-year survival of 40 per cent in all cases and 71 per cent cure in Stage I cases which constitute 23 per cent of the total cases.

TABLE V. CARCINOMA OF CERVIX. RESULTS OF TRANSVAGINAL X-RAY

AUTHOR	YEARS	TOTAL CASES	STAGE I		RESULTS IN PER CENT		FOLLOW- UP
			CASES	PER CENT	STAGE I	ABSO- LUTE	
<i>By the Use of a Single Large Vaginal Field.—</i>							
del Regato	1943-44	76	10	13	60	44	3 years
Caulk	1936-42	202	72	36	66	44	5 years
<i>By the Use of Multiple Small Vaginal Fields.—</i>							
Twombly and Chamberlin	1943-44	113	24	23	71	40	3 years

These scant threads of evidence suggest that, from the standpoint of results, the transvaginal application of x-rays to the single large field gives promise but shows no superiority over intracavity radium combined with x-ray. The multiple-field technique must be kept *sub judice* until more reports of results are available.

Last, the interstitial technique with radium needles has been employed by Donaldson,²⁵ Teahan and Weatherwax,²⁶ Covington,²⁷ Taylor and Twombly,²⁸ and Pitts and Waterman.²⁹ The latter report between the years 1936 and 1940 a five-year cure of 71 per cent in Stage I and an absolute rate of 43 per cent. At Sloane we have been attracted to this method by the relative ease with which adequate doses of radiation can be delivered to the lateral pelvic region and

have elaborated upon the technique of Pitts and Waterman by measuring the dose delivered in the tissues.³⁰ The immediate results in the Stage III cases in which this method has been used are striking. We have not employed it in Stage I cases.

Summary

Intracavity radium combined with external x-ray has been followed by steadily improving results reaching in the most recent reports generally a level of around 70 per cent five-year survivals in Stage I League of Nations and 40 per cent in all cases (absolute).

In this clinic, in 149 cases treated in the years 1939 to 1943 there was an absolute survival of 43 per cent (46 per cent relative), and in Stage I, 76 per cent (83 per cent relative, i.e., excluding patients not followed and those dying of intercurrent disease).

Radical (Wertheim) hysterectomy, the earliest treatment for cancer of the cervix, was generally abandoned twenty years ago because of high mortality and a low cure rate.

The results of the modern (revived) Wertheim hysterectomy are expressed in the following meager reports.

(1) Five-year survival in 34 cases (Stage I)	41 per cent
Five-year survival in 20 cases (Stage II)	50 per cent
(2) Five-year survival in 88 cases	64.7 per cent
(3) Five-year survival in 18 cases	38.9 per cent
(4) Three-year survival in 36 cases	77 per cent

The number of cases is obviously too small to form a basis for an evaluation of the method. The figures as they stand indicate that considerable improvement in results will be necessary before the radical operation can be offered as a substitute for intracavity radium combined with x-ray.

To accomplish this improvement the operation must be performed by surgeons with exceptional training and with exceptional operative facilities. Unless the procedure is so thorough as to need these extra facilities, it will fail as of old.

The transvaginal use of x-ray must be considered experimental until more evidence of its effectiveness is available. From the fragmentary evidence at hand, it is impossible to compare the results of the technique employing a single large field with those which follow the use of multiple small fields.

The interstitial use of radium has produced superior results in the hands of a few therapists who should continue to improve the technique since by it one can attain a high gamma roentgen dosage in the parametrium.

Conclusion

Today as twenty years ago the standard treatment of cancer of the cervix is by intracavity radium combined with external x-ray.

Other techniques—transvaginal x-ray, Wertheim hysterectomy, interstitial radiation—possibly preferable for special indications, must be further studied before they can be considered as routine procedures.

References

1. Müller, J. H.: Schweiz. med. Wehnschr. 76: 497-498, 1946.
2. Freund, W. A.: Berl. klin. Wehnschr. 15: 417, 1878. (Abst. Am. J. Obst., N. Y. 12: 200-205, 1879.)
3. Clarke, J. G.: Bull. Johns Hopkins Hosp. 52: 120-124, 1895.
4. Caldwell, E. W.: New York M. J. 76: 47-49, 1902.
5. Abbe, Truman: Washington M. Ann. 2: 363-377, 1904.
6. Lampe, I.: Am. J. Roentgenol. 58: 651-662, 1947.
7. Corsecaden, J. A., Kasabach, H., and Lenz, M.: Am. J. Roentgenol. 39: 871-887, 1938.
8. Heyman, J.: J. A. M. A. 135: 412, 1947.
9. Hynes, J. F.: Am. J. Roentgenol. 60: 368, 1948.
10. Kimbrough, R. A., and Muckle, C. W.: AM. J. OBST. & GYNEC. 56: 657, 1948.
11. Munnell, E. W., and Brunschwig, A.: Surg., Gynec. & Obst. 87: 343-348, 1948.
12. Shaw, Fletcher: Surg., Gynec. & Obst. 64: 332-337, 1937.
13. Read, C. D.: AM. J. OBST. & GYNEC. 56: 1021-1036, 1948.
14. Morton, D. G.: Am. J. Roentgenol. 57: 685-696, 1947.
15. Masson, J. C., and Judd, D. B.: J. Mt. Sinai Hosp. 14: 483-490, 1947.
16. Meigs, J. V.: Am. J. Roentgenol. 57: 679, 1947.
17. Köhler, H., and Haenisch, F.: Strahlentherapie 76: 342-360, 1947.
18. Taussig, F. J.: AM. J. OBST. & GYNEC. 45: 733-748, 1943.
19. Nathanson, I. T.: In: Meigs, Joe V., and Sturgis, Somers H., editors: Progress in Gynecology, New York, 1946, Grune & Stratton, chap. VIII, sect. 8, p. 388.
20. Caulk, R. M.: Radiology 52: 26-33, 1949.
21. del Regato, J. A.: Surg., Gynec. & Obst. 86: 480-486, 1948.
22. Wasson, W. W.: Radiology 40: 434-457, 1943.
23. Erskine, A. W.: Radiology 46: 458-459, 1946. Wisconsin M. J. 39: 184-187, 1940.
24. Twombly, G. H., and Chamberlin, J. A.: Radiology 52: 14-25, 1949.
25. Donaldson, M.: Brit. M. J. 2: 1039-1041, 1930.
26. Teahan, R. W., Wammock, H., and Weatherwax, J.: J. A. M. A. 120: 423-426, 1942.
27. Covington, E.: Surg., Gynec. & Obst. 82: 512-517, 1946.
28. Taylor, H. C., Jr., and Twombly, G.: Am. J. Roentgenol. 56: 513, 1946.
29. Waterman, G. W., DiLeone, R., and Tracy, E.: Am. J. Roentgenol. 57: 671, 1947.
30. Corsecaden, J. A., Gusberg, S. B., and Donlan, C. P.: Am. J. Roentgenol. 60: 522-534, 1948.
31. Hurdon, E.: Cancer of the Uterus, London, 1942, Oxford University Press.
32. Paterson, R., Tod, M., and Russell, M.: The Results of Radium and X-ray Therapy in Malignant Disease: Being the Second Statistical Report From The Holt Radium Institute, Manchester, Now Part of The Christie Hospital and Holt Radium Institute, Years 1934-1938 Inclusive, Assessed at 5 Years, and 1932 and 1933 Assessed at 10 Years. Compiled 1945, Edinburgh, E. & S. Livingstone, pp. 94-101.
33. Schmitz, Herbert: AM. J. OBST. & GYNEC. 55: 262, 1948.
34. Miller, N.: Univ. Hosp. Bull., Ann Arbor 14: 86-95, 1948.
35. Bowing, H. H., and Fricke, R. E.: J. A. M. A. 137: 935, 1948.
36. Richards, G. E.: Am. J. Roentgenol. 58: 783-797, 1947.
37. Karr, J. W.: N. Y. State J. Med. 49: 500-504, 1949.
38. Baud, Juliette: J. A. M. A. 138: 1138-1142, 1948.

Discussion

DR. FRANKLIN L. PAYNE.—As the program committee predicted, our distinguished guest has covered the clinical phase of cervical cancer thoroughly. In order to round out the subject of cervical malignancy, the opportunity was given to me to discuss the pre-clinical or the noninvasive phase of this condition. The discussion of noninvasive cancer of the cervix may be divided into three parts: its definition, its lethal potentialities, and its management. Described as a microscopic growth of the cervix that is confined to the surface epithelium, noninvasive cancer has many synonyms, such as: preinvasive, pre-clinical, intramucosal, intraepithelial, carcinomatoid, carcinoma in situ, and Bowen's disease of the cervix. The architectural and morphologic changes that suggest or denote this condition have been described adequately. While the recognition of these changes may indicate the presence of true noninvasive cancer, it has been pointed out by Te Linde that this is not always the case. Such a picture may mean any one of four things: first, the tissue may have been removed from the edge of a grossly invasive cancer; second, the biopsy may represent the surface or edge of a microscopically invasive cancer; third, the slide may tell the whole story, namely, that of a true intraepithelial carcinoma, or finally the cellular changes may not be sufficiently definite or extensive to permit a diagnosis without further study and even then doubt may persist. Often the decision between these

four possibilities requires more microscopic sections and many times the procurement of additional tissue from the patient. The importance of this decision justifies every additional effort, however, for the choice of therapy depends upon differentiation between the four possibilities. While opinions vary as to the clinical importance of the cellular changes in the latter two groups, evidence seems to be mounting that these alterations do represent cervical cancer in the noninvasive phase.

This evidence may be divided into two categories: that of hindsight and that of foresight. The former is seen in the published reports concerning the development of clinical cervical cancer years following biopsies that were misdiagnosed as benign originally. At least eight such occurrences have been recorded. The shortest span between the original biopsy and gross malignancy was two and one-sixth years and the longest interval was twelve and one-half years. After the appearance of the cancers, review of the original slides led to the unquestioned diagnosis of intraepithelial malignancy in every instance. As further hindsight evidence, recently we encountered a cervical epithelioma (Stage II) that developed thirty-seven years after a curettage and amputation of the cervix. The original microscopic slides were considered to be benign. Recent review of these slides revealed a strip of mucosa containing all of the changes that are now considered to indicate the presence of intramucosal epithelioma.

This hindsight evidence is convincing, but no more so than the foresight testimony offered by Te Linde and Galvin in a study of cervixes that were procured by total hysterectomy following the diagnosis of carcinoma *in situ* from biopsy material. They reported that upon subsequent section and microscopic study, fifteen of sixteen such cervixes showed "absolute histologic evidence of invasive carcinoma." As Foote and Stewart pointed out this evidence of invasion is unexpectedly high. The apparent crux of the matter lies in the definition of invasion. Some workers accept subepithelial extension and dipping into the cervical glands while others require that the basement membrane be penetrated by altered cells for the diagnosis of invasion. While we subscribe to the latter concept, we concede that upon some occasions we cannot positively eliminate the presence of invasion microscopically. Furthermore, we believe that the microscopically noninvasive lesions possess potentialities that indicate active management.

Proposals for this management have ranged from simple observation to radical surgery or intensive radiation. Simple observation was practiced unknowingly by those who reported the subsequent tragic development of full-blown cancer. Yet this policy still has its advocates. According to Foote and Stewart, "In a recent conference held under the sponsorship of the American Cancer Society . . . it was proposed . . . by a limited number of those in attendance . . . that clinicians be induced to follow cases diagnosed as carcinoma *in situ* of the cervix, institute no treatment, and await further development." The evidence already at hand proves that the need is not for passive observation, but for active diagnostic and therapeutic measures.

Observation, with repeated biopsies, has been suggested for those problems in which the definite diagnosis is impossible with the tissue at hand. It would seem better to obtain more tissue by scalpel conization or amputation and thorough endocervical curettage. Usually, this will settle the matter and permit the prompt institution of adequate therapy. It will avoid the agony of uncertainty and it will remove the tissue that already has shown at least a tendency to veer in the direction of malignancy. Furthermore, the trauma of repeated biopsies to such tissue might conceivably serve as a harmful growth stimulus.

Cervical conization is practiced by some. Its therapeutic weakness lies in its failure to remove sufficient tissue. This applies particularly to the upper endocervical mucosa along which early cervical cancer is prone to extend. As a diagnostic step to procure ample tissue for microscopic study, conization is recommended highly. Following a separate endocervical and endometrial curettage, the conization should be done with a scalpel and not by means of the high frequency current for the latter procedure may char the tissue beyond the possibility of detailed microscopic evaluation.

Trachelectomy has been recommended as both a diagnostic and a therapeutic measure. The plan consists of cervical amputation with multiple sections of the removed tissue. At this point the management diverges; some consider the amputation to be therapeutically adequate if no microscopic penetration is detected. Others rely upon amputation as the

final step even in the presence of early invasion, provided the line of excision lies well beyond the area of involvement. We do not subscribe to this policy. While trachelectomy, which rarely includes the whole cervix, may be effective if the lesion is truly noninvasive, the presence of even microscopic penetration indicates additional therapeutic measures. We use trachelectomy to obtain tissue for further study, but we do not depend upon this procedure as a means of treatment.

Total hysterectomy—abdominal—is the most widely used approach to noninvasive cervical cancer. In contrast to radiation, fortunately it permits ovarian conservation. While experience thus far is too limited for its clinical evaluation, this seems to be a reasonable approach provided every effort is made to disprove the presence of microscopic invasion prior to the operation. The existence of questionable invasion would seem to indicate more drastic measures.

Vaginal hysterectomy is less popular in America than in Europe in the treatment of cervical malignancy. The danger of dissemination from trauma to the cervix and parametrium plus the vigorous manipulation of the uterus, both of which are necessary in vaginal hysterectomy, seem to nullify its theoretic advantages.

The modified Wertheim operation, consisting of a total abdominal hysterectomy with excision of portions of parametrial and paracervical tissues as well as a liberal cuff of the upper vagina, has been performed by Te Linde. It permits the removal of a good deal more tissue than the routine operation, but it is both more hazardous and more difficult than the average procedure. We doubt that this much surgery is necessary if the lesion has been shown by previous study to be noninvasive.

The ultimate in the attempted surgical excision of cervical cancer, known as the radical Clarke-Reis-Wertheim procedure, seems to be increasing in popularity even to the point of its occasional application to the earliest cases. This procedure is unnecessary in proved noninvasive cancer, but in case of obvious invasion it may be indicated. Meigs in discussing cancer in situ says, "As most cases show invasive cancer perhaps the more radical Wertheim procedure should be advised." We believe that the need for such drastic measures usually can be proved or disproved by the liberal procurement of ample tissue for preliminary microscopic study. In case invasion is demonstrated the choice lies between this procedure and radiation therapy, but in the absence of invasion less formidable tactics should be employed.

Most cervical cancer that is actually or presumably noninvasive has been treated by surgical means. Radiation has a place, however, as a supplement to surgery following both extensive plastic procedures with amputation of the cervix and total hysterectomy when microscopic study reveals the presence of unsuspected early cancer.

While our personal experience with noninvasive cervical cancer is limited, the incidence of its recognition is increasing steadily. In our laboratory thirty-six specimens were diagnosed as carcinoma in situ, originally. Further study eliminated eighteen of these as showing either microscopic or more extensive invasion. This left eighteen apparent intramucosal lesions for treatment. Five of these patients received radiation, all of whom had experienced recent plastic repairs, with cervical amputation. Six were treated by total hysterectomy and five by the modified Wertheim procedure, some with ovarian conservation. Of the remaining two, one refused further treatment following conization and one is now six and one-half months pregnant for whom we plan cesarean section and total hysterectomy.

Because of the subject's infancy and many other factors that require consideration, aside from the presence of early cervical cancer, the treatment of this condition is not standardized. The following general plan seems to be advisable. First are the unexpected lesions that are discovered immediately after major operations. Following a plastic repair the demonstration of carcinoma in situ in an amputated cervix indicates thorough section of the cervix and endocervix. If this reveals no invasion or extension, prophylactic intracavitary radiation is advised. If it reveals definite or questionable invasion, a complete course of external and vaginal portal radiation is followed by the local application of radium in full dosage. Following a routine total hysterectomy, the unexpected discovery of noninvasive cervical cancer is met thus: if further sections prove the lesion to be truly

noninvasive, no further treatment is indicated. On the other hand, if detailed study reveals questionable or definite microscopic invasion, a complete course of radiation by external and vaginal portals is administered.

Next is the policy of management in planned diagnosis and therapy. In the operating room patients receive separate cervical and endometrial curettages with separate study of the curettages. At the same time a scalpel cone cervical biopsy is done. If noninvasive cancer is found, further study is conducted until the presence or absence of invasion is proved to the best of our ability. In outpatient or office practice, one or more cup biopsies are taken. Except in rare instances, when excessive bleeding necessitates cauterization of the biopsy site, the cervix is not cauterized until the pathologist's opinion is in hand. The report of "no cancer" indicates cauterization. That of "suspicious," or of cancer in situ, requires hospitalization for fractional curettage and careful scalpel conization under anesthesia. If further study reveals microscopic invasion, the treatment consists of either radiation or the radical Wertheim hysterectomy depending upon factors that are not relevant to this discussion.

In the definite absence of microscopic invasion we practice total hysterectomy with ovarian conservation for the younger patients and radiation for both the older patients and the poor surgical risks. This leaves a group in which the possibility of early invasion cannot be disproved microscopically, those with marked subepithelial extension or pronounced intraglandular dipping or questionable penetration of the basement membrane. For these we prefer the more drastic measures, either the modified Wertheim procedure or a complete course of external and intracavitary radiation.

Of course, this policy is subject to change. For the present the management of very early cervical cancer must entail a certain amount of trial and error, always to be tempered by full recognition of the growth characteristics and the lethal potentialities of the disease and tempered also by the earnest desire to subject the patient to only that which is necessary to promise complete eradication of the tumor. As follow-up data accumulates, both here and elsewhere, upon the results of particular types of therapy the pendulum may swing to more conservative therapeutic measures or it may swing in the opposite direction to routine radical management. In the field of clinical cervical cancer, the constant struggle for better results stimulates healthy differences of opinion with frequent changes in therapeutic policy and the same urge should promote similar differences and changes in the management of this disease in its preclinical stage.

DR. THEODORE EBERHARD.—There are a few things I wish to emphasize. Since I first became a student of Dr. Corscaden at the Presbyterian Hospital some fifteen years ago I have learned that once he discusses a subject there is very little you can add to it. The figures which he presented from other clinics, and his own figures, and particularly the figures presented over various periods of years emphasize to me one point. We have no new treatments. He showed the lady suspended from the gas light in 1903. We have learned how to use our instruments and improve techniques since then. The thing which impressed me is that in a serious condition such as this there is only one sort of person qualified to treat these cases. That is the man who is willing to take the time to become interested in taking care of these patients carefully and one who will not do that has no right to treat the patient. Those of you who have the facilities and who are interested in doing this work and doing it well and carefully can do good work and the rest should not try it. There are also differences in hospitals. If you know those institutions intimately, you know that where there are men who are interested and do careful work the best results are obtained. It is ability and careful work that count.

DR. CORSCADEN (Closing).—I am in complete agreement with what Dr. Payne has said about the early lesions and am very much impressed by the results of the transvaginal cone shown by Dr. Behney. I believe that Dr. Eberhard's statement is one of the most important. All of these techniques are difficult and call for painstaking effort whether it be adjusting radium tubes in their proper position or cleaning out the obturator fossa. Success bears a direct relationship to thoroughness. As for the earliest type of biopsy, Dr. Gusberg in our Clinic is working on a biopsy device which will be simple to use in an office.

CARCINOMA OF THE CERVIX

(University Hospitals, 1926-1942)

J. H. RANDALL, M.D., W. C. KEETTEL, M.D., H. C. WILLUMSEN, M.D., AND
J. W. SCOTT, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, University of Iowa)

BETWEEN July 1, 1926, and September, 1942, 983 patients with cervical carcinoma were treated at the University of Iowa Hospitals. This study presents an analysis of the results from irradiation therapy in this group. This seems especially timely in the light of recent reports advocating surgical treatment for a limited group of early carcinomas of the cervix.

Most of the patients were indigent and residents of Iowa. All cases with a diagnosis of carcinoma of the cervix have been included, regardless of whether or not they were treated. Most of the patients were hospitalized for treatment, but some received therapy as outpatients. All patients were thoroughly studied when first seen. This survey includes complete history, general physical examination, and the usual laboratory procedures. Soon after admission, one of the senior staff performed a thorough pelvic examination and classified the lesions according to their extent, by the Schmitz criteria. Biopsies were taken to determine the histologic type and to verify the diagnosis, even though many carcinomas were quite evident on examination. It was impossible to obtain biopsies in certain patients who had been treated prior to admission, because the local lesion had either disappeared or was not easily accessible. In these instances, the referring physician was requested to furnish pathologic reports from other hospitals or slides which could be studied at the University Hospital. All histologic material was reviewed by the Department of Pathology and/or the Department of Gynecology.

The clinical care of all patients was carefully supervised by the Gynecologic Staff. Deep x-ray therapy was under the supervision and direction of the Department of Radiology. Radium applications were made by the Gynecologic Staff in close collaboration with the Department of Radiology. There have been frequent consultations between the two departments relative to the type and amount of therapy to be employed. Joint staff meetings have been held periodically to discuss case records and review therapeutic results.

Arrangements were made for patients to return for progress examinations three months after treatment was completed, and every six months thereafter for the first two years. For the next three years the patients were seen yearly. The Social Service Department and the Tumor Clinic have been very helpful in tracing patients, obtaining reports from local physicians and relatives, and in making arrangements for follow-up examinations.

It has been possible to trace 99.5 per cent of the cases treated. Four patients out of a total of 983 had moved to distant states and could not be contacted. All patients not traced and those who died of intercurrent disease have been counted as cancer deaths.

Irradiation was employed almost exclusively although a few patients have been treated surgically. The plan of irradiation therapy has been altered from time to time as experience was gained. From 1926 to 1931, patients were given one or more applications of radium, followed by short courses of deep x-ray therapy. Occasionally the local lesion was largely destroyed by electrocautery, but this practice was discontinued because the resulting infection and slough evidently increased the radio-resistance of remaining tumor cells and frequently made radium application difficult and dangerous. The local lesion responds best to irradiation when least disturbed and traumatized.

In 1931, the plan of therapy was changed so that a course of deep x-ray therapy to the pelvis was given first, followed immediately or a few weeks later by radium application to the local lesion. Eight to twelve weeks later another course of deep x-ray was given if the skin could tolerate it.

In 1937, the present method of therapy was instituted. This consists of a course of deep x-ray therapy to the pelvis through six to eight skin portals, two anterior and two posterior 15 by 20 cm., two lateral 15 by 10 cm., two gluteal 10 by 10 cm., and in some cases a perineal port. The following factors are used: 200 kv., target distance 50 cm., and a filter of 2 mm. of copper, or its equivalent. The dosage to each port at any one treatment is 200 r. measured in air. The total dosage varies from 10,000 to 25,000 air roentgens. The average dosage delivered to the parametrial regions is 3,500 to 4,000 roentgens. While the patient is receiving x-ray therapy, her general condition is improved as much as possible through correction of dietary deficiencies, blood transfusions, administration of parenteral fluids, vaginal douches, and, in recent years, the employment of antibiotics for obvious infection. Patients tolerate therapy best when their general condition is excellent, and poorest when they are cachectic.

Late in the course of x-radiation or at its conclusion, radium is applied locally. Two 25.0 mg. tubes of radium screened with 1.5 mm. of platinum and 1.0 mm. of rubber are placed in tandem in the uterine cavity, and six 10.0 mg. tubes screened with 1.5 mm. of platinum are placed against the cervix in a brass block. The intravaginal radium is spread as much as possible in the transverse axis of the vagina by using different sizes of blocks, and is concentrated in the lateral fornices to increase the dosage to the parametrium. The radium is left in place for fifty to sixty hours, or until 5,500 to 6,500 mg. hr. have been given. The bowel and bladder are carefully packed away for their protection and the latter is kept empty by continuous drainage.

Irradiation sickness, a troublesome sequel to x-ray therapy, has been empirically treated by oral administration of viosterol or sodium chloride, or by large parenteral doses of thiamine, vitamin B complex, or pyridoxin hydrochloride. In earlier cases an ionization chamber was placed over the patient's head, but its use has been discontinued. Vitamin B complex appears as effective as anything that has been tried for control of irradiation sickness. Diarrhea has been treated by dietary measures, powdered opium or a combination of lead acetate and opium, and retention enemas of oil or starch paste. Severe skin reactions are expected where the radiation has been pushed to tolerance. Patients and staff are instructed to keep all irritating substances, such as soap, alcohol, adhesive tape and antiseptics, from irradiated skin areas. Nothing is applied to the skin except bland oils or petroleum jelly.

Blood counts, blood smears, and hemoglobin determinations are done repeatedly. Blood transfusions are given freely to combat anemia, leucopenia, or severe cachexia. In patients with any suspicion of urinary tract invasion, cystoscopy and/or intravenous pyelograms are done to determine the involvement. Proctoscopic examinations are used to determine the extent of rectal injury. Symptoms suggestive of metastases to lungs or bones are studied by x-ray films.

The Schmitz classification has been used to indicate the stage of the disease, because of its simplicity and workability, and because it emphasizes the early lesion. At present, patients are grouped according to both the Schmitz and the League of Nations classifications. This will permit comparison of our results with those of most other clinics, since they are the most commonly used systems of classification.

Carcinoma of the cervix occurred most commonly between the ages of 40 to 49 years, when most women are passing through the climacteric. Only one patient was under 20 years of age. The incidence increased up to 40 to 50 years and then slowly declined, becoming relatively insignificant after the age of 70 years. The oldest patient was 79 years of age, the youngest 17 years and the average age was 48.5 years. Approximately one-half the patients were postmenopausal.

There were 959 white and 24 Negro patients. This is about the ratio of white to Negro patients in the general hospital admissions. The majority were indigent, but a few were private or part-pay patients.

Seven hundred seventy-five patients (89.1 per cent) were parous, 108 (10.9 per cent) were nulliparous and 83 of these had never been pregnant. These figures indicate that parity has favored the development of cervical carcinoma only to a slight extent, if consideration is given to the relation of nulliparous to parous women in the general population.

From July 1, 1926, to Sept. 1, 1942, 983 carcinomas of the cervix were seen at the University Hospitals clinics. Forty-seven (4.7 per cent) received only general care, chiefly because they were in the hopeless, or Stage IV, group and it was felt inadvisable to subject them to heavy irradiation. One hundred eighty-three (18.6 per cent) received only deep x-ray therapy. Most of this group were advanced cases with badly ulcerated and infected local lesions, making radium application difficult and unfeasible. Thirty-eight (3.8 per cent) received only radium. Some of these had extremely early lesions that were not subjected to deep x-ray therapy because parametrial or lymphatic spread was unlikely. The others with more advanced lesions either refused or failed to return for x-ray therapy, or were unable to tolerate it. Five hundred eighty-four patients (59.4 per cent) were treated with combined deep x-ray therapy and radium. The five-year survival rate for this group was 37.6 per cent.

TABLE I

AGE GROUPS		NO. OF CASES
0-19		1
20-29		38
30-39		190
40-49		318
50-59		243
60-69		156
70-79		37
Total		983
Youngest patient	17	
Oldest patient	79	
Average age	48.5	

TABLE II. SUMMARY OF TREATMENT AND SURVIVAL OF 983 CASES OF CARCINOMA OF THE CERVIX, JULY 1, 1926, TO SEPT. 1, 1942

TYPE OF TREATMENT AT STATE UNIVERSITY OF IOWA	STAGE I		STAGE II		STAGE III		STAGE IV		ALL STAGES		SURVIVAL	
	CASES	5 YR.	CASES	5 YR.	CASES	5 YR.	CASES	5 YR.	TOTAL	%	5 YR.	%
No treat- ment	0	0	0	0	4	0	43	1	47	4.7	1	2.1
X-ray alone	1	1	13	7	71	8	98	1	183	18.6	17	9.2
Radium alone	16	13	6	0	10	2	6	0	38	3.8	15	39.7
X-ray and radium	34	31	116	74	342	112	92	3	584	59.4	220	37.6
X-ray plus transvagi- nal x-rays	0	0	14	6	54	15	30	3	98	9.9	24	24.4
Wertheim hysterec- tomy	2	1	2	1	0	0	0	0	4	0.3	2	50.0
Wertheim hyst. and x-ray	0	0	3	2	3	1	0	0	6	0.5	3	50.0
Other treat- ment	13	13	6	4	2	0	2	0	23	2.3	17	73.9
Total	66	59	160	94	486	138	271	8	983	100	299	30.4
Per cent of total	6.8	89.0	16.0	58.7	49.4	28.3	27.0	2.0				

Ninety-eight (9.9 per cent) were treated entirely with deep x-ray, through the skin and, transvaginally, to the local lesion. The latter involved five transvaginal exposures of 1,000 r. each. The factors used were 200 kv., 0.5 mm. copper and 1.0 mm. aluminum filtration, target distance 40 cm., and a cylindrical speculum to fit the vagina. The transvaginal treatments were given twice weekly near the end of the regular therapy. A detailed account of the use of transvaginal therapy in this clinic has been presented by Elkins.¹ Twenty-four patients (24.4 per cent) treated in this manner survived five years. Results with this variation of therapy have not been so good as those with x-ray and radium, probably because only unfavorable cases were originally selected for transvaginal treatments. At present, alternate patients are given transvaginal therapy, in order to permit its better evaluation in the treatment of cervical carcinoma.

Four patients were treated by radical hysterectomy (Wertheim) alone, and six by this operation followed by deep x-ray. Five of the ten patients survived five years, a five-year salvage of 50.0 per cent.

For the entire group of 983 cases, the over-all absolute five-year survival was 30.4 per cent. Only by comparing absolute survivals with those of other clinics can the effectiveness of any therapy be evaluated.

The time from July 1, 1926, to Sept. 1, 1942, has been divided into two periods, namely, July 1, 1926, to Sept. 1, 1937, and Sept. 1, 1937, to Sept. 1, 1942, since it allows estimation of the ten-year salvage for the first period and also permits evaluation of our present method of treatment which was begun in 1937. There were 562 cases in the former period and 431 in the latter.

Of the 562 cases in Group I, 432 were treated entirely at this clinic, with 128 five-year survivals (29.6 per cent) and 104 ten-year survivals (20.4 per

TABLE III. 432 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA HOSPITAL, JULY 1, 1926, TO SEPT. 1, 1937

TYPE OF TREATMENT	STAGE I			STAGE II			STAGE III			STAGE IV			TOTAL		SURVIVAL				
	SURVIVAL		CASES	SURVIVAL		CASES	SURVIVAL		CASES	SURVIVAL		CASES	SURVIVAL		CASES	SURVIVAL			
	5 YR.	10 YR.		5 YR.	10 YR.		5 YR.	10 YR.		5 YR.	10 YR.		5 YR.	10 YR.		CASES	%	CASES	%
No treatment	0	0	0	0	0	0	1	0	0	0	0	5	0	0	6	1.3	0	0	0.0
X-ray alone	0	0	0	6	1	1	31	3	3	3	40	0	0	0	77	17.8	4	5.2	4
Radium alone	4	2	2	3	0	0	2	0	0	0	3	0	0	0	12	2.9	2	16.6	2
X-ray and radium	18	16	14	59	39	34	199	52	39	42	0	0	0	0	318	73.0	107	33.6	87
Wertheim hysterectomy	1	1	1	2	1	1	0	0	0	0	0	0	0	0	3	0.6	2	66.6	2
Wertheim hyst. and x-ray	0	0	0	3	2	1	1	1	1	0	0	0	0	0	4	0.9	3	75.0	2
Other treatment	7	7	6	4	3	1	0	0	0	0	1	0	0	0	12	2.7	10	83.3	7
Total	30	26	23	77	46	38	234	56	43	91	0	0	0	0	432	100.0	128	29.6	104
Per cent of total	6.9	86.0	76.0	17.8	59.0	49.0	54.0	23.9	18.0	21.0	0	0	0	0					

TABLE IV. 130 CASES OF CARCINOMA OF THE CERVIX PARTIALLY TREATED PRIOR TO ADMISSION TO STATE UNIVERSITY OF IOWA HOSPITAL, JULY 1, 1926, TO SEPT. 1, 1937

TYPE OF TREATMENT AT STATE UNIVERSITY OF IOWA	STAGE I			STAGE II			STAGE III			STAGE IV			ALL STAGES		SURVIVAL			
	SURVIVAL			SURVIVAL			SURVIVAL			SURVIVAL			STAGES		5 YR.		10 YR.	
	CASES	5 YR.	10 YR.	CASES	5 YR.	10 YR.	CASES	5 YR.	10 YR.	CASES	5 YR.	10 YR.	TOTAL	%	CASES	%	CASES	%
No treatment	0	0	0	0	0	0	2	0	0	9	0	0	11	8.4	0	0	0	0
X-ray alone	1	1	1	3	3	2	14	3	3	34	0	0	52	40	7	13.4	6	11.5
Radium alone	0	0	0	1	0	0	2	1	1	2	0	0	5	3.4	1	20	1	20
X-ray and radium	1	1	1	4	1	1	24	6	3	29	0	0	58	44.6	8	13.7	5	8.6
Wertheim and x-ray	0	0	0	0	0	0	2	0	0	0	0	0	2	1.5	0	0	0	0
Other treatment	1	1	1	1	0	0	0	0	0	0	0	0	2	1.5	1	50.0	1	50.0
Total	3	3	3	9	4	3	44	10	7	74	0	0	130	99.4	17	13.1	13	10
Per cent of Total	2.3	100.0	100.0	6.9	44.0	33.0	33.8	22.7	15.9	56.9	0	0						

cent). The remaining 130 patients had received some treatment prior to admission. The majority had been inadequately treated and were admitted here with advanced lesions; 74 (57 per cent) belonged in Stage IV. Many of the group were given additional x-ray and/or radium therapy. The absolute five-year salvage was 13.1 per cent and the ten-year survival 10.0 per cent. Three hundred eighteen patients were treated entirely here with x-ray and radium, and the relative five-year survival was 33.6 per cent. In general, we feel that patients do much better when they receive full-tolerance dosages during the initial treatment. It is not advisable to reirradiate areas which previously received full tissue tolerance doses.

In the second period, there were 421 patients, 337 of whom were treated entirely at this hospital, with an absolute five-year salvage of 39.4 per cent. Most of this group (54.4 per cent) were treated with combined x-ray and radium with a relative five-year survival of 51.9 per cent. Eighty-four had been treated with some form of irradiation before admission. The majority belonged in Stages III and IV; and the absolute five-year survival was 25.0 per cent.

Combined x-ray and radium treatments gave 33.6 and 51.9 per cent five-year survivals in the two groups, respectively.

During the two periods, 501 patients have been treated with combined x-ray and radium under our direct control. This is a group sufficiently large to justify study of the various factors which might be related to end results. From Table VII it is obvious that the stage of the disease is the most important factor in end results. There were 33 Stage I cases with 87.8 per cent survivals and 108 in Stage II with a survival rate of 64.8 per cent. The five-year salvage of the Stage III and IV cases was 32.5 and 3.5 per cent, respectively. Thus it is evident that the stage of the disease is the most important factor in prognosis. It is doubtful if a Stage IV case is ever cured although we report survival of 3.5 per cent of this group. Most of the survivors were probably erroneously classified as Stage IV cases because of inflammatory rather than neoplastic infiltration of the parametrium.

TABLE V. 337 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA HOSPITAL, SEPT. 1, 1937, TO SEPT. 1, 1942

TYPE OF TREATMENT	STAGE I		STAGE II		STAGE III		STAGE IV		ALL STAGES		SURVIVAL	
	CASES	SUR-VIVAL 5 YR.	CASES	SUR-VIVAL 5 YR.	CASES	SUR-VIVAL 5 YR.	CASES	SUR-VIVAL 5 YR.	TOTAL	%	5 YR.	%
No treatment	0	0	0	0	0	0	8	0	8	2.4	0	0.0
X-ray alone	0	0	1	0	16	0	14	0	31	9.0	0	0.0
Radium alone	11	10	2	0	5	1	0	0	18	5.3	11	61.0
X-ray and radium	13	12	50	32	106	50	14	2	183	54.4	96	51.9
X-ray plus transvaginal x-rays	0	0	14	6	49	12	25	2	88	26.0	20	22.0
Wertheim hysterectomy	1	0	0	0	0	0	0	0	1	0.3	0	0.0
Other treatment	5	5	1	1	1	0	1	0	8	2.4	6	75.0
Total	30	27	68	39	177	63	62	4	337	99.8	133	39.4
Per cent of total	8.9	90.0	20.0	57.0	52.0	35.5	18.0	6.4				

TABLE VI. 84 CASES OF CARCINOMA OF THE CERVIX PARTIALLY TREATED PRIOR TO ADMISSION TO STATE UNIVERSITY OF IOWA HOSPITAL, SEPT. 1, 1937, TO SEPT. 1, 1942

TYPE OF TREATMENT AT STATE UNIVERSITY OF IOWA	STAGE I		STAGE II		STAGE III		STAGE IV		ALL STAGES		SURVIVAL	
	CASES	SUR-VIVAL 5 YR.	CASES	SUR-VIVAL 5 YR.	CASES	SUR-VIVAL 5 YR.	CASES	SUR-VIVAL 5 YR.	TOTAL	%	5 YR.	%
No treat-ment	0	0	0	0	1	0	21	1	22	26.1	1	4.5
X-ray alone	0	0	3	3	10	2	10	1	23	27.3	6	25.0
Radium alone	1	1	0	0	1	0	1	0	3	3.6	1	33.0
X-ray and radium	2	2	3	2	13	4	7	1	25	29.0	9	36.0
Xray plus transvagi-nal x-rays	0	0	0	0	5	3	5	1	10	12.0	4	40.0
Other treat-ment	0	0	0	0	1	0	0	0	1	1.2	0	0.0
Total	3	3	6	5	31	9	44	4	84	99.2	21	25.0
Per cent of total	3.5	100.0	7.0	83.3	36.9	29.0	52.0	9.0				

TABLE VII. 501 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA HOSPITAL WITH X-RAY AND RADIUM. EFFECT OF CLINICAL STAGE ON FIVE-YEAR SURVIVAL, JULY 1, 1926, TO SEPT. 1, 1942

	CASES	PER CENT	5 YEAR SURVIVAL	PER CENT
Stage I	33	6.6	29	87.8
Stage II	108	21.5	70	64.8
Stage III	304	60.7	99	32.5
Stage IV	56	11.2	2	3.5
Total	501	100.0	200	39.9

The improvement in end results has not been due entirely to increase in the number of early cases, since Table VIII shows that Stages I and II constituted 21.7 per cent of the cases in the first period and 24.9 per cent of those in the second period. The absolute five-year survival for all patients in the first period was 25.7 per cent and in the second 37.0 per cent. This improvement of almost 50 per cent cannot be attributed to the increase in early cases but must be due to improved therapy.

There were 39 adenocarcinomas (7.8 per cent) in the group of 501 cases treated with x-ray and radium, a higher incidence than most clinics report. This is probably due to inclusion of some advanced cases of carcinoma of the body with involvement of the cervix among the cervical carcinomas. The five-year salvage was ten (25.6 per cent). The adenocarcinomas did not respond as well to irradiation as the more common squamous-cell lesions. The epidermoid carcinomas were classified histologically into three groups, namely, epidermoid I, or spinal cell; epidermoid II, or transitional cell; and epidermoid III, or spindle cell. Most of the lesions were of the transitional-cell type (55.8 per cent). The spindle-cell (immature or anaplastic) lesions responded slightly better than the more mature tumors, but the difference is insignificant. It appears from these data that the histologic grade of epidermoid cervical carcinoma has very little effect upon the end results of radiation therapy. It is also our experience that grading epidermoid carcinomas into more than three groups is impractical and inaccurate. Some decision should be reached among clinics con-

cerning the treatment of body carcinomas that involve the cervix, and their grouping as to site. Because of their poorer prognosis, obviously, they lower the survival rate of the group in which they are placed, whether cervical or body. In most reported statistics of cervical and body malignancies, no mention is made of the uterus in which adenocarcinoma involves both corpus and cervix.

TABLE VIII. 983 CASES OF CARCINOMA OF THE CERVIX TREATED BETWEEN JULY 1, 1926, AND SEPT. 1, 1942

	JULY 1, 1926, TO SEPT. 1, 1937				SEPT. 1, 1937, TO SEPT. 1, 1942					5 YEAR SURVIVAL	
	TOTAL CASES		SURVIVAL		TOTAL CASES		SURVIVAL				
	CASES	%	CASES	%	CASES	%	CASES	%	TOTAL	CASES	%
Stage I	35	6.1	30	85.7	31	7.5	29	93.5	66	59	89.3
Stage II	89	15.6	51	57.3	71	17.4	43	60.5	160	94	58.7
Stage III	282	49.3	66	33.4	204	49.6	72	35.2	486	138	28.3
Stage IV	166	29.0	0	0.0	105	25.5	8	7.6	271	8	2.9
Total	572	100.0	147	25.7	411	100.0	152	37.0	983	299	30.4

TABLE IX. 501 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA WITH X-RAY AND RADIUM. EFFECT OF HISTOLOGIC GROUPING ON FIVE-YEAR SURVIVAL

TYPE OF CARCINOMA	TOTAL	PER CENT	5 YEAR	PER CENT
Adeno	39	7.8	10	25.6
Epidermoid I (Spinal)	84	16.8	34	40.4
Epidermoid II (Transitional)	279	55.7	111	39.8
Epidermoid III (Spindle)	99	19.7	45	45.4
Total	501	100.0	200	39.9

The lesions were classified according to the gross morphology of the local tumor into exophytic, those which grew outwardly into the vagina, and endophytic, those growing inwardly. There were 317 of the former and 184 of the latter. In general, exophytic carcinomas responded better to irradiation than did the endophytic. The five-year survival percentages were 45.1 and 30.9, respectively. It would seem that exophytic lesions respond better to irradiation chiefly because the tumor has not infiltrated so deeply into the parametrial tissues.

Most of the 501 cases were in the 40 to 49 year age group. Younger patients responded poorly, the five-year survival being 25 per cent, as did those above the age of 70. Many of the older patients could not tolerate a full course of therapy. Patients in the age group 50 to 59 years responded best.

There were 52 patients (5.2 per cent) who had had subtotal hysterectomies. Twenty-four either had had the carcinoma at the time of operation or symptoms of cancer developed within the following year. The remaining 28 patients developed symptoms of cervical carcinoma more than a year after subtotal hysterectomy. The five-year survivals for the two groups were 20.8 and 37.8 per cent, respectively. In the presence of cervical carcinoma, subtotal hysterectomy, by delaying correct diagnosis, definitely decreases the chance for cure, but when this operation antedates the carcinoma by some years the response to therapy is similar to that of patients with intact uteri.

Sixty-seven patients (6.8 per cent) had latent syphilis. The incidence of syphilis among University Hospital patients is approximately 4.0 per cent. There were 16 five-year survivals in this group (23.8 per cent).

In 29 patients, the carcinoma was discovered during pregnancy or the puerperium; the five-year survival was 20.7 per cent (6 cases).

TABLE X. 501 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA HOSPITAL WITH X-RAY AND RADIUM. EFFECT OF GROSS ANATOMIC SITE ON FIVE-YEAR SURVIVAL, JULY 1, 1926, TO SEPT. 1, 1942

	NUMBER	PER CENT	5 YEAR	PER CENT
Exophytic	317	63.2	143	45.1
Endophytic	184	36.8	57	30.9
Total	501	100	200	39.9

TABLE XI. 501 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA WITH X-RAY AND RADIUM. EFFECT OF AGE ON FIVE-YEAR SURVIVAL, JULY 1, 1926, TO SEPT. 1, 1942

AGE	NO. OF CASES	PER CENT	5 YEAR SURVIVAL	PER CENT
Less than 20	1	0.2	0	0
20-29	20	4.0	5	25
30-39	99	19.7	42	42
40-49	161	32.1	63	39
50-59	125	24.9	57	45
60-69	79	15.8	28	35
70-79	16	3.2	5	30
Total	501	99.9	200	39.9

There were 604 patients (61.4 per cent) who had no febrile reaction during treatment with 36.4 per cent surviving five years, as against 214 (21.7 per cent) who had fever with 16.3 per cent five-year survivals. One hundred one (10.2 per cent) had fever only during radium therapy with a 35.6 per cent five-year survival, while among 52 with fever during both x-ray and radium therapy, the survival rate was 9.6 per cent. It appears that infection during x-ray therapy is more significant than during the application of radium. It would seem that the presence of infection in the local tumor increases the radio-resistance of cancer cells. However, many infected carcinomas are ulcerated and far advanced, which probably also adversely affects the end results. Fevers were considered significant when the temperature was 100.4° F. on two or more consecutive days.

TABLE XII. 501 CASES OF CARCINOMA OF THE CERVIX TREATED ENTIRELY AT STATE UNIVERSITY OF IOWA HOSPITAL WITH X-RAY AND RADIUM. INCIDENCE OF MAJOR COMPLICATIONS

MAJOR COMPLICATIONS	TOTAL	PER CENT
Proctitis (severe)	34	6.7
Cystitis (severe)	17	3.3
Rectovaginal fistula	13	2.5
Fracture (femur)	10	1.9
Stricture (bowel)	8	1.5
Parametritis	6	1.0
Vesicovaginal fistula	5	.9
Ureteral obstruction	5	.9
Peritonitis	3	.5
Both recto- and vesicovaginal fistula	1	.19
Total	102	20.3

Table XII shows the total number of complications in the 501 patients treated with combined x-ray and radium. One hundred two patients (20.3 per cent) had either mild or severe complications. The majority developed some degree of proctitis and colitis, but in 34 the irritation of the lower bowel was

severe enough to necessitate hospitalization. Most of the irritation appeared during x-ray therapy but was aggravated by radium. Seventeen patients (3.3 per cent) had severe cystitis, and a few had persistent interstitial changes in the bladder. There were 13 (2.5 per cent) rectovaginal fistulas and five (0.9 per cent) vesicovaginal fistulas in the development of which irradiation played a prominent part. In many cases it was difficult to determine whether the fistulas were due to advancement of the disease or to irradiation. Ten patients (2 per cent) developed fractures of the femoral neck secondary to irradiation, but the majority have recovered completely. The administration of a cancerocidal dose of irradiation to the pelvis inevitably produces damage to normal tissues. By giving maximal primary therapy the increased salvage will more than compensate for the complications encountered.

Table XIII shows that the primary mortality in 983 cases from irradiation therapy was 1.7 per cent (17 cases). All of these fatalities were due directly to radium or x-ray. Five of the patients who died as a result of treatment had early carcinomas. Ten fatalities were due to perforation of the uterus during radium application with subsequent peritonitis, and seven to bowel injury or severe irradiation sickness produced by x-ray.

TABLE XIII. PRIMARY MORTALITY IN 983 CASES OF CARCINOMA OF THE CERVIX, STATE UNIVERSITY OF IOWA HOSPITAL, JULY 1, 1926, TO SEPT. 1, 1942

AGE	TOTAL	GROUPING				MORTALITY	
		I	II	III	IV	DUE TO RADIUM	DUE TO X-RAY
20-29	2	1	0	0	1	0	2
30-39	5	0	2	3	0	3	2
40-49	4	0	0	2	2	3	1
50-59	3	0	1	1	1	3	0
60-69	3	0	1	1	1	1	2
Total	17	1	4	7	5	10	7
Per cent of Totals	1.7	5.8	23.5	41.6	29.4	58.0	41.0

Discussion

The end results from combined x-ray and radium treatment of cervical carcinoma have been good, if not better, than those reported from surgery. Victor Bonney's^{2, 3} absolute five-year survival rate was 25 per cent when all operable cases were subjected to Wertheim radical hysterectomy. His considerable experience with this operation suggests that he could have improved his results only through reduction of the primary mortality. Although Meigs⁴ has done a considerable number of radical hysterectomies with no primary mortality, this operation could certainly not be performed by the average operator without an appreciable risk. The mortality of the operation has been definitely lowered through improved surgical technique, better anesthesia, blood transfusions, and antibiotics. If Victor Bonney's primary mortality were entirely eliminated, his five-year survivals would have been increased to thirty-five per cent, approximately what has been attained through irradiation.

Considering the fact that most cervical carcinomas are advanced when first seen, irradiation must continue to be the principal type of therapy. If it can be shown that absolute results are better by treating early cases surgically and ad-

vanced ones with irradiation, it will be necessary to employ the latter only for inoperable cases. The value of the radical operation for patients in whom the local lesion has not responded to maximum irradiation or for those who develop a new malignancy in the cervix or upper vagina cannot be disputed.

The recent attempt to make the Wertheim operation more radical, so that its scope can be extended, is still in the experimental stage with no significant data on its value in increasing the final salvage.

It would seem that more emphasis should be placed upon the early diagnosis of carcinoma, since the stage of the disease is the most important factor in end results. When cytologic laboratories are established to make vaginal-smear evaluation generally available, it is not beyond the realm of possibility that most cervical cancers will be diagnosed in early stage when the disease can be treated effectively with either surgery or irradiation.

Conclusions

1. From July, 1926, to Sept. 1, 1947, 983 cases of cervical carcinoma were treated chiefly by irradiation therapy at State University of Iowa Hospitals with an absolute five-year survival rate of 30.4 per cent.
2. During the years 1926 to 1937, the absolute five-year survival rate was 25.7 per cent, but increased to 37.0 per cent for the years 1937 to 1942.
3. There has been marked improvement in end results from irradiation therapy due to improvement in technique.
4. The most important single factor in end results is the stage of the disease.
5. The histologic character of epidermoid carcinomas has little effect upon final results.
6. Patients who are young or senile and those who are febrile or have an inverting type of growth generally respond less well to irradiation.
7. Complications are inevitable when irradiation is given to the limits of tolerance.
8. There is a definite primary mortality of 1 to 2 per cent from irradiation treatment of cervical cancer to the point of tissue tolerance.

References

1. Elkins, H. B.: J. Iowa M. Soc. 37: 196, 1947.
2. Bonney, Victor: AM. J. OBST. & GYNEC. 30: 815, 1935.
3. Bonney, Victor: J. Obst. & Gynaec. Brit. Emp. 48: 421, 1941.
4. Meigs, Joe Vincent: Am. J. Roentgenol. 57: 679, 1947.

PREGNANCY AND LABOR EXPERIENCES OF ELDERLY PRIMIGRAVIDAS

EDWARD G. WATERS, M.D., F.A.C.S., AND HENRY P. WAGER, M.D.
JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

WE ARE concerned in this presentation with the problem of the elderly patient pregnant for the first time. There are few physicians who have not been confounded by her questions. Not many of us possess the personal experience to answer adequately the queries we receive and our opinions are often based upon archaic and untrue information. These women want to know if and how their labor and parturition experiences may differ from early childbearing years. For instance, does the fact of late primiparous childbearing necessitate obstetrical management radically differing because of genital tract obsolescence? Are vaginal operative procedures much more common, much more dangerous, and is cesarean section a common or even usual manner of terminating such pregnancies? Are pregnancy disorders and complications more frequent and more dangerous, is the labor itself more severe, more prolonged, and followed by a greater likelihood of invalidism? In the answer to these and other questions are found the survival probability for mother and child, the chance for further childbearing, the validity of concern over late pregnancy by patient and physician, and finally, a guide to the safest manner of insuring maternal and infant life.

Source of Material

The analysis of experiences and results embodied in this paper offers answers to these and other questions, for it concerns all of the elderly primiparas delivered during a ten-year period at the Margaret Hague Maternity Hospital, with the findings contrasted with those of a comparable group of definitely young primiparas.

The childbearing life of women may be divided into three spans or trimesters. The first decade of 15 to 25 years comprises definitely young primiparas. The intermediate group is 25 to 35 years, and in the elderly group all are over 35 years. Since the majority of elderly primiparas would naturally fall into the earlier years of the third trimester as shown by our experience, a statistical aberration might arise by a comparison with the intermediate group or, under some conditions, the clinic material as a whole. Therefore, the experiences of all of the elderly group are tabulated for comparison with an equal number of young primiparas selected at random and taking proportionate numbers of cases for each year of the ten-year period. Where sampling would be inadequate, as with cesarean sections, the comparisons are with the general clinic incidence.

It is difficult to see the interpretive value of statistical data dealing solely with elderly primiparas. Even if compared to clinic material as a whole, a considerable portion of the intermediate group might contain influencing factors not too dissimilar from a group of elderly patients. With comparative analysis,

however, it is believed that a reasonably accurate picture of the actual labor and parturition experiences is obtained and may be contrasted with probable experiences of their missed early childbearing decade. In other words, what added risks have these patients assumed by having their pregnancies twenty years later than the optimum age group?

The answer is sought in this review of 56,396 deliveries in a ten-year period at the Margaret Hague Maternity Hospital. There were 649 primiparas over 35 years of age, of whom 639 were white, eight Negro and two Mongolian. In the prorated random selected group of 649 primiparas under 25 years used for comparison, there were 630 white, 19 Negro.

The various tables are in general self-explanatory and subsequent remarks will accentuate only their more significant and pertinent components.

Effect of Age on the Disorders and Complications of Pregnancy

Since the manner of parturition is frequently conditioned or dictated by disorders or complications of the pregnancy itself, irrespective of mechanical factors, it may be well first to consider the ante- and intrapartum happenings. Pernicious vomiting of pregnancy has been considered a common complication in elderly primiparas, but this is not verified by our experience. There were only three severe cases in the elderly group compared to six in the young group. Consideration of the toxemias of pregnancy, however, shows pre-eclampsia and eclampsia occurring with twice the frequency, and nephritis also much more commonly encountered. Hypertension is seen about twice as often. This is in accord with previously published data from this clinic (Chesley), where toxemia incidence is higher in all groups of patients with pre-existing renal disease and hypertension. The effect of aging upon the vascular system thereby acquires considerable significance, and is of distinct importance in prognosis. As might be expected, the higher toxemia frequency materially influences the operative rate. Since these data show pregnancy toxemia to be more than twice as frequent as in the young, they indicate the need in the elderly for constant and careful supervision during the last third of pregnancy.

TABLE I

TOXEMIAS	35 YEARS AND OVER	%	25 YEARS AND UNDER	CLINIC INCIDENCE
	NO.			%
Pre-eclampsia	34	5.2	15	3.01
Eclampsia, all	3	0.46	2	0.26
Hypertension, essential	9	1.3	5	1.1
Nephritis	6	0.9	1	0.22
Pernicious vomiting	3	0.46	6	0.35
Acute yellow atrophy	2	0.3	0	
Unclassified late toxemias	20	3.1	27	2.2
Total	77		56	

The fetus itself is subjected to the hazard of abortion, which is three times as frequent, and fetal death before labor (2.16 per cent), but there is nothing to indicate any marked increase in abnormal fetation, in contrast to common opinion. Total fetal salvage is approximately the same as with young primiparas, even though premature labor is a much more frequent occurrence.

TABLE II

ABNORMAL TERMINATION OF PREGNANCY	35 YEARS AND OVER	25 YEARS AND UNDER
Early abortion (1st trimester)	15	6
Late abortion (2nd trimester)	13	4
Premature delivery	31	24

The hemorrhagic diseases of the last trimester of pregnancy materially influence the manner of delivery. It is of more than ordinary importance, therefore, that we know, within reason, the probability for these complications occurring in late pregnancy. We find abruption of the placenta and placenta previa frequent in the elderly, and reference to Table III will indicate their frequency with respect to young primiparas. Antepartum hemorrhage of undetermined cause, meaning vaginal bleeding of undetermined origin, probably includes certain cases of partial abruption or of low placental implantation. In the group of twenty-three elderly primiparas with parturition complicated by antepartum hemorrhage, the operative incidence obviously must be high. These twenty-three cases contrast with five in the young group who hemorrhaged before parturition. Reasons may be found in the data on pregnancy toxemia, nephritis, and hypertension, which directly influence the occurrence of abruption and also the increase with advancing years of the myopathies which make abnormal placentation more likely. Hemorrhagic complications are encountered twice as often as in the general clinic, and four times that in the young patient. It is well, however, to remember that these absolute ratios still leave such complications as relatively infrequent occurrences (2.9 per cent) among elderly parturients.

TABLE III

HEMORRHAGIC COMPLICATIONS	35 YEARS AND OVER	25 YEARS AND UNDER
Abruption of placenta	11	0
Placenta previa	8	2
Antepartum bleeding (cause ?)	4	3
Hydatidiform mole	1	0

Effect of Age Upon the Mechanics of Parturition

Pelvic types unfavorable for normal vaginal delivery occur four times as often in the elderly group. This fact does not lend itself to easy interpretation, but it has been noted repeatedly in other analyses. The relationship of relative sterility and late pregnancy is present in some cases but is not so sufficiently constant as to account for the wide differences noted. The factors of prolonged sterility and infertility with genital hypoplasia are of no more significance than in younger patients, and when pregnancy occurs they present essentially the same problems relative to labor and its manner of termination, irrespective of age. Less favorable are malpresentations, noted twice as often in the elderly group, a finding of significance when considering the termination of labor. There was no absolute prolongation of labor, and the more frequent rupture of membranes before onset of labor did not influence labor duration markedly. There is nothing in the data obtained nor in the author's experience to indicate that late childbearing is accompanied by dystocia dependent upon rigidity of the perineal tissues, the pelvic fascia, or inflexibility of the pelvic ligaments. Long labors are more noted by the attendant when they occur but they are not more frequent. There is no increase in postpartum uterine atony, blood loss or hemorrhage, in spite of the increased number of myopathic uteri. Complications dependent upon the latter would seem to require some other factor, as previously revealed, in producing conditions conducive to hemorrhage.

TABLE IV

PRESENTATION AND DELIVERY	35 YEARS AND OVER	25 YEARS AND UNDER
Normal, vertex	367	480
Abnormal	208	81
Occipitotransverse, occipitoposterior	169	58
Breech	29	20
Transverse	6	2
Face	4	1

TABLE V

MEMBRANES	35 YEARS AND OVER	25 YEARS AND UNDER
Spontaneous rupture, before labor	135	83
Spontaneous rupture, first stage	177	222
Artificial rupture, before labor	11	3
Artificial rupture, first stage	36	28

There is no significant change in weight or measurements of the newborn. The expected increase in ovular defects is represented in the increased number of abortions, and the aging uterus produces an increase in antepartum intra-uterine stillbirths. But fetal salvage of babies born at term, as previously disclosed, was almost the same as with the young group. The increase in mal-presentations augmented the operative incidence to 33 $\frac{1}{3}$ per cent as against 20 per cent, presented in Table VIII. But again, the figures on fetal injury and survival fail to show any increased danger to the fetus through judicious use of mechanical means to expedite or facilitate delivery in these patients. Our direct observation of a large number of elderly parturients fails to reveal any notable increase in mental or emotional effects, or interference with normal recuperation or puerperal involutional changes.

Complicating Systemic Disease and Disability

Heart disease is one of the most serious of all medical complications. Its incidence in the elderly group will be observed to be almost identical with that of the young primiparas. This is not as paradoxical as it might seem. Since the life span of cardiac patients is in large measure limited to the earlier years, it follows that many would not survive to become pregnant for the first time beyond the age of 35 years. It is also probable that many of those surviving would not marry, or if they did, would not conceive or carry. Therefore, these figures, which seem to indicate that heart disease as a complication of pregnancy is not seen more often in the elderly than in the young primipara, can be taken as representative of true occurrence. Certainly a group as large as this study entails should show such a difference if it were existent or significant. The same reasoning applies to diabetes although a better survival rate is progressively being obtained and we might find more patients reaching the late childbearing years. However, the known failure of adequate diet and insulin therapy to prevent vascular degeneration in the aging diabetic probably accounts for the failure of many of these patients either to become pregnant or to carry to term. The high toxemia incidence and vascular sclerosis make pregnancy infrequent and highly dangerous beyond 35 in any diabetic.

TABLE VI

MEDICAL AND SURGICAL COMPLICATIONS	35 YEARS AND OVER	25 YEARS AND UNDER
Anemia, Secondary	9	4
Cholecystitis; cholelithiasis	2	0
Goitre	1	0
Hyperthyroidism	1	0
Appendicitis	1	0
Urinary tract infections	8	14
Cyst, labia	6	0
Fibromyoma of uterus	22	1
Neoplasm, breast	1	0
Intercurrent infections	8	7
Diabetes	1	0
Heart disease	13	11
Myomectomy, with cesarean section	7	0

Neoplasms involving the generative tract are far more common as age progresses. This shows up especially in the case of fibromyomas of the uterus, a condition almost absent from the young group, but extremely common in the last trimester of the childbearing years. What effect it has upon the mechanism of labor and manner of delivery will require further comment.

Manner of Delivery

Most significant figures are seen in Tables VII and IX. Forceps applications were made twice as often in the elderly as in the young patient. Most marked variations are noted in forceps for outlet dystocia and pelvic arrest, four times more common in the elderly patient. Even more striking are the statistical data on cesarean section, done five times as often. Here comparison was not made with the random selected group of young primiparas because this would not be suitable, inasmuch as the general cesarean incidence was under three per cent. The general clinic incidence was used because while the 649 young primiparas selected from the larger group would be included with the similar number of elderly primiparas, in a group of nearly 60,000 deliveries this would not be sufficient to produce a significant statistical aberration.

TABLE VII. INDICATIONS FOR OPERATIVE DELIVERIES

(1) PELVIS (RECORDED BY X-RAY)	35 YEARS AND OVER	25 YEARS AND UNDER
Flat (platypelloid)	9	2
Small gynecoid	20	15
Android	25	7
Anthropoid	28	4
Total	82	28
(2) OTHER FACTORS		
Rigid coccyx	2	3
Relative disproportion	104	26
Uterine inertia	9	5
Pathologic rigidity of cervix	4	0
Fetal distress	8	3
Total	127	37

TABLE VIII. OPERATIVE DELIVERY, VAGINAL

FORCEPS	35 YEARS AND OVER NO.	%	25 YEARS AND UNDER	CLINIC INCIDENCE %
Low, outlet dystocia	91	14.02	34	3.48
Low, prophylactic	114	17.5	104	12.6
Median	13	2.0	4	.727
Median with rotation	51	7.8	17	2.66
High	2	0.3	0	0
To aftercoming head	14	2.15	6	.876
Breech extraction	14	2.15		
Version, podalic	1	0.15		
Dührssen's incisions	2	.31		.045
Craniotomy, cleidotomy	2	.31		.01

TABLE IX. CESAREAN AND MORTALITY DATA. PRIMIPARAS OVER 35 YEARS, TEN-YEAR PERIOD

CESAREAN TYPE	NO. CASES	INCIDENCE %	GENERAL CLINIC INCIDENCE %	MORTALITY	%
Classical	5	0.77	0.175	1	
Low segment	73	11.25	1.704	1	
Extraperitoneal	27	4.16	0.541	1	
Hysterectomy	1	0.15	0.038		
Other	1	0.15	0.012		
Total	107	16.4	2.9	3	2.8

Socio-economic Factors

There are a number of influencing conditions of pregnancy and parturition in this group which do not easily lend themselves to tabulation, but which recur constantly in any experience and at least must be mentioned. The attitudes developed toward pregnancy vary widely but in general are in accord with the accepted ones of motherhood. The older patient, in the absence of complications, has no more nor greater ills in early pregnancy, to induce disquiet toward her status. The most disturbing states tend to develop after discharge to her home. If she has married late, the dislocation is less. If childbearing came late in married life, then the interference with long-established routine is notable, and markedly augmented should infant care become complicated. The older patient is psychologically less well adapted to handle the minor ills and care for the baby, and the degree of apprehension increases as the ovulating years become fewer. The natural increase in physical impairments and illnesses beyond 35 years and the 10 per cent fewer babies living and viable at term are inductive to increased nervous tension and lessening of the normal resiliency to "trouble." Worry is somewhat provoked by the need for extra supervision during pregnancy, especially due to the increase in toxemia incidence and hemorrhagic complications.

In spite of the above, however, the vast majority of these elderly primiparas under good counsel approach maternity with a magnified keenness of appreciation and a thoroughly stabilized and rational attitude.

TABLE IX A. MORBIDITY AND MORTALITY. TEN-YEAR PERIOD

	NUMBER	%	CLINIC %
All deaths in clinic	145	0.26	0.23
Deaths over 35—primiparas	8*	1.2	
Cesarean deaths	3	2.8	1.2
Morbidity	72	11.0	5.0

*Deaths: cardiac 3, coronary 1 (cesarean section), toxemia and postpartum eclampsia 1, peritonitis 1, operative hemorrhage and shock 1 (cesarean section), pneumonia 1 (cesarean section). Two of the three cesarean deaths were preventable.

TABLE X

BLOOD LOSS	35 YEARS AND OVER	25 YEARS AND UNDER
Slight (not over 200 c.c.)	438	453
Moderate (200 to 500 c.c.)	190	174
Severe (500 to 1,000 c.c.)	18	22
Very severe (over 1,000 c.c.)	3	0
Postpartum hemorrhage	9	16

TABLE XI. COMPLICATIONS OF THIRD STAGE

PLACENTAL ANOMALIES	35 YEARS AND OVER	25 YEARS AND UNDER
Adherent placenta	2	2
Retention of placenta	4	8
Retention of membranes	2	0
Manual removal	7	5
Placenta accreta	0	1

TABLE XII

ABNORMAL FETAL CONDITIONS	35 YEARS AND OVER	25 YEARS AND UNDER
Congenital anomalies	23	16
Birth injuries	13	7
"Icterus neonatorum"	4	7
Atelectasis	2	2
Intercurrent diseases	23	17

TABLE XIII

INFANT (CONDITION ON BIRTH)	35 YEARS AND OVER		25 YEARS AND UNDER	
	NO.	%	NO.	CLINIC INCIDENCE %
Living at term	511	78.6	519	89.4
Premature, viable	23	3.5	23	5.14
Premature, nonviable (under 6½ months)	3	.464	2	5.46
Dead before labor	14	2.16	3	1.08
Dead before labor, monstros	1	.154	0	
Dead during labor	11	1.69	8	1.00
Neonatal deaths	16		13	
Total fetal loss	45		26	

TABLE XIV

ANESTHESIA	35 YEARS AND OVER		25 YEARS AND UNDER	
Chloroform		3		4
Ether		48		131
Nitrous oxide		92		108
Nitrous oxide-ether		222		231
Novocain infiltration		2		3
Novocain spinal		190		56
Other combinations		26		27
Anesthesia deaths		0		0

TABLE XV

ANALGESIA	35 YEARS AND OVER		25 YEARS AND UNDER	
Barbiturates		85		63
Morphine—scopolamine		266		276
Other combinations		230		245
Not recorded		68		65

Discussion

The age at which one becomes an elderly primipara necessarily must be arbitrary. With respect to conception and childbearing, a patient is not young one day and old the next and thereby in a group requiring or receiving attention which may radically differ. The years of childbearing are rather constant, between 15 and 45. Biologically the early years would naturally constitute those when primiparity would have the highest incidence. We would expect economic and social factors to produce a statistical shift away from the very early years and show a gradual rise in primiparous incidence to a maximum during the third decade of life. Actually, as we have seen, this occurs. At the other end of the span, the age factor should not materially influence birth incidence until the last third of the childbearing years. While the aging process varies widely in its rate of invasion in various individuals, it is appreciated that at 35 its effects are generally patent, though seldom extensive. Thirty-five would seem to be the choice optional year for indicating when aging becomes directly of concern in pregnancy management and prognosis. It marks the half-time of life as well as the last third of menstrual life, and the closing years of fruitful marriage or of pregnancy possibilities in the recently married. It is highly desirable from a standpoint of critical analysis to have a commonly designated and accepted age-group for late primiparity and in this analysis it is established at 35 years and older.

Consideration is also given the effect of age upon pregnancy, of pregnancy upon the aging individual, and the effects of deferring primiparity into the last ten years of childbearing life. The patient and her doctor are stirred by the potential of increased trouble applicable to delayed first pregnancy.

The effect of age upon pregnancy is noted in the increase in systemic disease concurrent with aging, notably vascular disease and its complements, the toxemias of pregnancy. The well-recognized increase of pregnancy and fibroid coexistence in the older group is again seen, although there is a notable lack of interference with late pregnancy by fibroids. The high incidence of abortion may be explained by increased myopathy, the altering hormonal balance, and peripheral vascular changes. The greatest threats in any pregnancy are hemorrhage, infection, toxemias, heart disease. Bleeding leading to abortion and that associated with placenta previa and abruption is met with increasing frequency as aging progresses. The toxemias are twice as numerous in the important categories. The rate for heart disease is fairly constant for all groups and understandably so, for the per-year death loss to 35 reduces a high potential cardiac loss, and patients with severe cardiac disease not marrying or not conceiving before 35 are less likely to become or stay pregnant. Morbidity from intra- and postpartum sepsis is no higher, excepting for a sharp rise in puerperal endometritis. This may be associated largely with the very much higher incidence of operative termination of labor (q.v.).

The membranes rupture more often before the onset of labor, but this seems to influence the labor outcome mainly in those coming to cesarean section, and the extraperitoneal route is then chosen. Premature delivery is not common and induction of labor infrequently needed.

Pelves of restricted capacity and abnormal presentations involve the principals often. These notably influence the operative incidence. Excluding purely prophylactic use, low forceps were required four times and midforceps three times as often as in the general clinic. The cesarean incidence was five times the general clinic rate, with extraperitoneal section used in one-fourth of these operations.

There is no single reason for the high vaginal and abdominal operative incidence. Certainly it is not to be found in the hours in labor (no longer), the days hospitalized (no more), blood loss (no greater), the birth weight of the infant, or antepartum morbidity. The major contributing factors are the increase, in this series, in malpresentations, restricted pelvic capacity, high toxemia rate, placental abruption and previa. In outlet forceps, most of the applications were to shorten the second stage in the interest of the fetus and because of its high social value, since the duration of labor was not generally prolonged when delivery was effected. The repetitious inference that most elderly primiparas have rigid perineae was not borne out by experience, nor shown by the indications for employing forceps. There is nothing in this series nor in the writer's personal observations to show that there is any significant obstructive change in the character of the maternal soft parts while the patient is still within the childbearing years. The high number of midforceps deliveries was due in large measure to the transverse and posterior occipital presentations, resolved mostly with Kielland forceps.

The very high incidence of cesarean section requires some study. It is evident that the indications must be widely broadened in this elderly group to provide an incidence of over 16 per cent when the general clinic rate was about 3 per cent. The factors previously referred to operate largely in the causation of this high figure, but listed in more than half of the cesarean operations are correlated indications which are statistically diverse and intangible, and may be assembled under the heading, "high social value of the child." This, in a primipara over 35, is a highly salutary and commendable inclusion which tips the scale to cesarean section when there are any factors in the pregnancy or imminent parturition which prejudice the likelihood for fetal survival. In our opinion it is the most potent of aggregate indications when more than one are given. It designates conservative salvage from what may be conceivably the

only pregnancy in the elderly patient's experience. When cesarean section offers an excellent chance against a moderately good chance for fetal survival in this group, it is generally elected in our clinic.

It will be noted that there were 145 deaths (0.26 per cent) in the hospital during the 10-year period, and thirty-six or one-fourth of these were gravidas over 35 years of age. In nearly half of these, diseases coincident with or worsened by aging were factors as causes of death. This is certainly an indicant, if one were needed, that having babies after 35 is less safe than in the first thirty years of childbearing. But only 8, or 5.5 per cent, were elderly primiparas and of these only three followed cesarean section. While four might be considered as dependent directly or indirectly upon aging, these figures certainly do not establish elderly primiparity as a grave maternal life threat, whether the delivery is normal or operative. The risk is obviously greater, as might be expected, but the differential between old and young primiparas is certainly not remarkable.

Without repeating endlessly, it may be said that this experience indicates a favorable outlook for the elderly patient who comes to her first pregnancy in good physical condition, without cardiac, vascular, or degenerative disease. She is more likely to have certain complications of late pregnancy, notably toxemia and hemorrhage, and there is a rather good probability for some type of operative termination of labor. Although the possibility of fetal loss prior to labor is higher, she has an equally good chance for survival of her baby if the pregnancy carries to term successfully. If one considers the progressive yearly population death loss, first pregnancy does not constitute a great hazard for her after 35 years. Pregnancy after 35 may be contemplated with reason, approached with intelligence and confidence, and managed before, during, and after parturition with complete awareness of the hazards, adequate preparation for threatened complications, and conservative intervention in the interest of the lives involved.

Sommerville, I. F., Marrian, G. F., and Clayton, B. E.: The Effect of Diethylstilbestrol on Urinary Excretion of Pregnanediol and Endogenous Oestrogen During Pregnancy, The Lancet, p. 680, April 23, 1949.

This experiment was carried out to re-examine a 1946 report that the administration of stilbestrol during pregnancy results in increased pregnanediol excretion. In 1947, a second group reported that stilbestrol given to nondiabetic pregnant women failed to produce such an increase, but this experiment did not include accurate base levels of pregnanediol excretion, and the stilbestrol doses were higher than originally recommended.

One nondiabetic, and three diabetic pregnant women were given stilbestrol in doses similar to those originally prescribed. In every instance administration of stilbestrol was followed by a sharp fall in pregnanediol excretion, promptly reversible by stopping the drug. This discrepancy may be due to the gravimetric assay method used in the original study, since the supposedly pure sodium pregnanediol glucuronide probably contained other materials, notably sodium stilbestrol glucuronide. This experiment also failed to demonstrate any gross change in endogenous estrogen excretion after stilbestrol administration.

IRVING L. FRANK.

MAJOR GYNECOLOGIC OPERATIONS IN THE PATIENT OVER 50 YEARS OF AGE*

JOHN C. WEED, M.D., AND J. R. MIGHELL, M.D., NEW ORLEANS, LA.

(From the Departments of Obstetrics and Gynecology, Tulane University School of Medicine
and the Department of Obstetrics and Gynecology, Ochsner Clinic)

THE increasing span of human life is responsible for the growing number of women seeking medical aid for gynecologic ailments beyond the age of 50 years. Whereas the life expectancy of a female child born at the turn of the century was 51 years, advances in medical and surgical care have increased this to 69.5 years, almost the biblical "three score and ten." At the present time, a woman 40 years of age may expect 34.4 more years of life and at the age of 65, 14 more years. This expectancy gradually decreases with age but even at 90 years there is still an expectancy of two to three more years of life. It has been estimated that the growing longevity will increase the population over 65 years of age from 6.8 per cent (1940) to about 14.4 per cent by 1980. Such a rise will indubitably augment the problem of surgical management in many elderly women.

The problems posed by the geriatric patient are gradually becoming of greater interest to the medical profession. This is evidenced by various reports in the literature on the surgical risk and the nutritional requirements of the aged. In fact, interest has been sufficiently great to warrant publication of a periodical devoted exclusively to the aged (*Geriatrics*).

Few reports in the literature have dealt with the gynecologic aspects of geriatrics.^{1, 2, 3} Probably the most significant study is the one by Lash,¹ who presented an analysis of 313 gynecologic operations in women over 60 years of age. Our interest in this problem was stimulated by his report as well as by the apparent reluctance of some surgeons to advise necessary surgical procedures in the aged. We chose the age of 50 years rather than 60 as the beginning of old age because many women between 50 and 60 years of age present essentially the same problem as those over 60. Degenerative changes in the human mechanism may begin at any age but by the fiftieth year such changes frequently have become obvious. Often a patient of 55 years may exhibit the same degree of senility as one ten years older.

Material

This report is based on an analysis of 237 cases of hysterectomy performed on women between the ages of 50 and 78 years by members of the gynecologic staff of the Ochsner Clinic from the time of its founding, Jan. 1, 1942, until Jan. 1, 1948. All were private patients of the Caucasian race. Operations were performed at Touro Infirmary and Foundation Hospital. The age distribution is shown in Table I and requires no further comment.

*Presented before the meeting of the New Orleans Obstetric and Gynecologic Society, March 23, 1948.

TABLE I. AGE DISTRIBUTION IN 237 HYSTERECTOMIES

AGE	TOTAL	SUBTOTAL	VAGINAL	TOTAL CASES
50-54	86	1	29	116
55-59	35	4	23	62
60-64	8	1	17	26
65-69	6	0	12	18
70-74	4	0	7	11
75-80	1	0	3	4

The principal symptoms of which these patients complained are listed in Table II. A large number had multiple complaints, of which vaginal bleeding was the most prominent. This varied from spotting to frank hemorrhage.

TABLE II. GYNECOLOGIC COMPLAINT

SYMPTOMS	TOTAL	SUBTOTAL	VAGINAL
Prolapse	0	0	45
Pelvic pain	50	3	24
Backache	32	2	39
"Bearing down"	4	0	32
Leucorrhea	82	2	68
Urinary frequency	40	2	76
Urinary burning	0	0	46
Urinary incontinence	12	0	76
Menopausal bleeding	39	0	9
Postmenopausal bleeding	74	4	31
Abdominal tumor	12	0	1

The pathologic lesions demonstrated at operation are listed in Table III. The high incidence of endometrial activity as well as polyp formation in women of 50 or more years is of interest. It has been estimated that the incidence of endometrial cancer is three and one-half times greater in those who have functional bleeding at the menopause.⁴ Malignancies of the internal genitals were encountered in 17.3 per cent of the series, a slightly higher incidence than is reported by Lash or Manahan (14.0 per cent). In three cases the malignancies were double primary neoplasms (carcinoma of the endometrium [one case] associated with leiomyosarcoma [two cases], squamous-cell carcinoma of the cervix, or primary carcinoma of the Fallopian tube). The presence of endometriosis (23 per cent) still detectable in this age group is of interest, but its relationship to complaints is questionable. Leiomyomas occurred in 39.1 per cent of all cases. Not all were of considerable size, but the clinical findings indicate that asymmetric enlargement of the uterus was present in 27.4 per cent of all cases. Of the twenty-one patients to whom radium was administered for functional bleeding years before, seven continued to have fibroids of significant size as long as twenty-six years later. One woman, in whom castration was done by roentgen ray for functional bleeding, continued to have pelvic pain from large fibroids. This is at variance with a current report on the treatment of fibromyomas with radium.⁵

It is of some interest to point out that two cases of tuboovarian abscess were found in postmenopausal women. These were pyogenic in origin, not mycotic or tuberculous.

Because prolonged operative time might increase the hazard of surgical treatment, the time of operation was determined. In cases suitable for vaginal hysterectomy 31 per cent required less than forty-five minutes and 89 per cent less than one hour. In the abdominal series, the duration of operation was somewhat longer, 45 per cent requiring one hour or less and 79 per cent be-

tween sixty and ninety minutes. In four cases in which the Wertheim hysterectomy was done, from two to three hours were required. It should be stated that colpectomy was also performed in two of the vaginal hysterectomies and that in addition to abdominal hysterectomy the following procedures were performed: perineorrhaphy in nine cases, cholecystectomy in one case, and inguinal hernioplasty in one case. There was, however, no correlation between operative time and morbidity.

TABLE III. MICROSCOPIC PATHOLOGY

	TOTAL	SUBTOTAL	VAGINAL	TOTAL CASES
Chronic cervicitis	58	0	36	94
Chronic cystic cervicitis	61	0	49	110
Cervical polyps	11	0	7	18
Granuloma of cervix	0	0	1	1
Endometriosis of cervix	0	0	1	1
Carcinoma of cervix, squamous	8	2	2	12
Atrophic endometrium	39	4	67	110
Benign endometrial hyperplasia	59	0	19	78
Endometrial polyps	22	0	14	36
Carcinoma of endometrium	21	0	0	21
with squamous carcinoma of cervix	1	0	0	1
with primary carcinoma of tube	1	0	0	1
with leiomyosarcoma	1	0	0	1
Endometriosis, myometrial	22	0	22	44
Endometriosis, pelvic	11	1	0	12
Leiomyomas	66	2	25	93
Pyometrium	1	1	1	3
Chronic salpingitis	48	1	2	51
Hydrosalpinx	1	0	1	2
Tuboovarian abscess	2	0	0	2
Fibroma of ovary	4	0	0	4
Benign ovarian cyst	10	0	0	10
Primary ovarian carcinoma	4	1	0	5
Chronic appendicitis	31	1	0	32

TABLE IV. POSTOPERATIVE COMPLICATIONS

TYPE	TOTAL	SUBTOTAL	VAGINAL	TOTAL CASES
Urinary	4	0	33	37
Pelvic abscess	0	0	2	2
Postoperative bleeding	0	0	2	2
Wound infection	1	1	0	2
Phlebothrombosis	1	0	1	2
Cut ureter with ureterovaginal fistula	0	0	1	1
Intestinal obstruction	1	0	0	1
Pulmonary embolus	1	0	1	1
Pulmonary	3	0	0	3
Postoperative convulsion (grand mal)	0	0	1	1
Auricular fibrillation	1	0	0	1
Multiple extra systole	1	0	0	1
Pelvic hematoma	1	0	0	1
Ileus	2	0	0	2

The postoperative complications of the entire series are listed in Table IV. The high incidence of urinary complications in the vaginal hysterectomies has led to the routine use of an indwelling catheter for decompression of the bladder for forty-eight hours. Thrombophlebitis or phlebothrombosis, detected in but two cases (one a fatality from pulmonary complications), was an insignificant cause of morbidity. The standard of morbidity in this series was a temperature

of 101° F. at any one time postoperatively, or 100.4° F. or more for two consecutive days. In view of such a rigid standard the morbidity of this group (Table V) does not seem excessive. If the group is divided into patients above and below 60 years of age, the contrast in morbidity is worthy of note. In the vaginal group, 42.8 per cent were 60 years of age or older, and 41 per cent of these were morbid, as contrasted to 59.6 per cent of those from 50 to 59 years. In the small series of total hysterectomies on patients over 60, there was a morbidity rate of 15.8 per cent as contrasted to 28 per cent for those from 50 to 60 years of age. These figures are merely suggestive since the number of cases is too small to be statistically significant.

TABLE V. MORBIDITY AND MORTALITY

	TOTAL	SUBTOTAL	VAGINAL
Morbidity	38 (27.1%)	2 (33%)	47 (51.6%)
Mortality	1	0	0

TABLE VI. MEDICAL COMPLICATIONS

	TOTAL	SUBTOTAL	VAGINAL	TOTAL CASES
Hypertension:				
140/90 or above	74	1	50	125
200	3	1	4	8
Obvious heart disease	7	0	9	16
Abnormal electrocardiogram	8	1	10	19
Diabetes mellitus	7	0	7	14
Hemiplegia	0	0	1	1
Duodenal ulcer	1	0	1	2
Hepatic disease	0	0	1	1
Diverticulosis	1	0	0	1
Obesity	50	3	30	83

Discussion

When the aging woman appears with gynecologic complaints requiring surgical treatment, the first consideration must be the patient as a whole. Women in their fifties may be more senile, more debilitated, and more incapacitated from degenerative processes than some of their older sisters. This may be due in part to a life of ceaseless struggle but, on the other hand, it may simply be the result of passive surrender or inability to continue to compete with their contemporaries. The prematurely aged woman often is mentally depressed, has a hopeless outlook, and considers her present complaint as the last straw. Obviously, these women are the poorest surgical risks. Their confidence must be gained, and several visits may be required before this can be accomplished. Fear of death as a rule is far outweighed by fear of cancer. Reassurance must be coupled with a confident attitude on the surgeon's part.

The hazards of surgical treatment are not greatly increased with age, as our small series indicates. Again, the individual patient must be considered. Is the life expectancy such that a major procedure is justified? Will the substitution of a minor procedure provide relief at less risk? The life expectancy must be weighed against the patient's comfort and her will to live. Many of our older patients considered comfort in their remaining years to be worth any reasonable risk. Because of recurrence of bleeding after many years' cessation, we believe that hysterectomy is the procedure of choice if the organ is diseased or if pronounced degrees of prolapse are present. Only if the risk is great should minor procedures such as radium application or the Le Fort operation be substituted.

In this series, eighteen of the patients in whom postmenopausal bleeding was a prominent complaint (Table II) had received radium therapy from two and one-half months to twenty-six years before. Three of these had malignancies (one cervical, one endometrial, and one ovarian) subsequent to radiation. Three others had no bleeding, but had abdominal tumors requiring exploration. Had the major procedure been performed originally, the subsequent risk of these patients would have been considerably lessened. It has been our experience that the more extensive procedure involves little more time and not much more shock than plastic operations. The patient, too, has an undeniable sense of relief from the knowledge that the organ has been removed.

Proper evaluation of the patient should include a thorough medical and laboratory investigation. An estimation of the cardiac reserve and electrocardiographic and renal function studies should be done to eliminate bad risks from prolonged surgical procedures. The presence of obvious heart disease or of abnormal electrocardiograms should lead to caution but should not be a deterrent to necessary surgical treatment. It will be noted that 56 per cent of the patients in our series had some degree of hypertension (Table VI). Eight per cent of our patients had significantly abnormal electrocardiograms, but all were well compensated, and the surgeon was forewarned to avoid overloading the vascular tree. Electrocardiography was performed in only 23 per cent of our cases, but the electrocardiogram was abnormal twice as often after the age of 60. The associated problem of hypertension parallels the findings by electrocardiography although the difference between those above and those below 60 is not as great.

The nutritional status of these women is of great significance. Much has been written about the importance of nitrogen balance and adequate vitamin intake. This problem is not as great as in cases of gastro-intestinal malignancy but should not be overlooked. Over 80 per cent of the entire series were "well nourished or obese." No instance of emaciation was encountered. Obesity (150 pounds or more) was recorded in 35 per cent of cases, and the weight exceeded 200 pounds in about 10 per cent. The problem of preparation, then, in these old women is chiefly one of weight reduction and vitamin supplementation.

The incidence of diabetes in our series (5.9 per cent) is considerably higher than the expected rate for this group of women. Joslin⁶ placed the incidence of diabetes in persons 55 to 65 years old as 1 in 50 cases. The diabetic patients in our series were treated by an internist by diet, or diet and insulin.

As a preparatory measure, adequate cornification of the vaginal tract should be induced. This is especially true in the older women when a vaginal operation is anticipated. Healing is improved and local complications may be avoided. Stilbestrol, in 0.5 mg. suppositories, for ten days preoperatively is all that is necessary. We have had no experience with penicillin suppositories as a pre-operative measure. Reduction of a completely prolapsed organ, with or without a pessary, considerably reduces both edema and superficial inflammation, so that operative facility is increased and healing enhanced.

Lyons⁷ emphasized the importance of pre-operative restoration of blood volume in severely depleted individuals. Only 21 per cent of our series had less than 4,000,000 red blood cells per cubic millimeter, and the group above 60 years of age as a whole was less anemic than those below 60 years. This is probably the result of cessation of copious vaginal bleeding in these women.

The choice of anesthesia seems to be one of individual preference. In contrast to Te Linde's⁸ preference for Pentothal and Mussey's⁹ for inhalation anesthesia, regional block (lumbar) anesthesia, with or without a supplement, was the procedure of choice in 73 per cent of all cases. More recently, it has been exceptional to use inhalation anesthesia alone in any case. It is customary also to replace blood volume lost during operation immediately, rather than to depend upon other fluids.

Postoperatively the elderly group of patients should be especially encouraged to maintain physical activity and adequate ventilation of the lungs. It is only by these measures that postoperative pulmonary complications and intravascular clotting can be eliminated. Early ambulation is encouraged to the utmost. Within twenty-four hours the patient should be able to sit up in bed and should exercise the legs frequently and by forty-eight hours she should be out of bed. The presence of an indwelling catheter does not prevent ambulation, and in fact, ambulation and sitting on a commode to void allow early removal of such a catheter.

It has been our practice, especially in vaginal and abdominal hysterectomies, if the cervix is greatly diseased, to administer penicillin prophylactically in doses of 30,000 to 50,000 units at the time of operation and every three hours thereafter for the next thirty-six to forty-eight hours. This therapy has lowered the morbidity rate appreciably in the more recent cases of the series.

The one fatality in this series occurred twenty-one days postoperatively in a patient subjected to vaginal hysterectomy. Severe cystitis required replacement of an indwelling catheter and prolonged rest in bed. Evidence of intravascular clotting was detected five days before the fatal accident. Surgical consultation suggested compression bandages and continued observation. Total massive pulmonary embolism occurred after improvement was reported. This case, however, is listed as a preventable death.

It should be emphasized that the patient between 50 and 59 is too often regarded as a better surgical risk than the patient over 60. Perhaps this is true, but there is not a significant difference, and the age difference alone might lower the surgeon's guard in the former case and thus provide a false sense of security. On the other hand, the figure of 60 years or more stimulates the surgeon to seek a more thorough preparation and closer observation following operation.

Conclusions

1. The surgeon need not be afraid of performing major gynecologic procedures on patients over 60 years of age, as these patients tolerate such operations well and perhaps even better than the patient between 50 and 60 years.

2. The incidence of serious pelvic disease in patients over 60 years of age suggests that more radical operations should be done at earlier ages, rather than palliative medical procedures in these cases.

3. With proper preoperative and postoperative care the morbidity and mortality rates in these patients are not greater than in younger women.

References

1. Lash, A. F.: *AM. J. OBST. & GYNEC.* 53: 766-775, 1947.
2. Manahan, C.: *J. Philippine M. A.* 22: 323-326, 1946.
3. Kosmak, G. W.: *AM. J. OBST. & GYNEC.* 44: 897-910, 1942.
4. Corscaden, J. A., and Gusberg, S. B.: *AM. J. OBST. & GYNEC.* 53: 419-431, 1947.
5. Crossen, R. J., and Crossen, H. S.: *J. A. M. A.* 133: 593-599, 1947.
6. Joslin, E. P.: *Treatment of Diabetes Mellitus*, Philadelphia, 1944, Lea & Febiger.
7. Lyons, C., and Mayerson, H. S.: *J. A. M. A.* 135: 9-10, 1947.
8. Te Linde, R. W.: quoted by Kosmak.³
9. Mussey, R. D.: quoted by Kosmak.³

THE EFFECT OF ADOPTION ON FERTILITY AND OTHER REPRODUCTIVE FUNCTIONS

FREDERICK M. HANSON, M.D., AND JOHN ROCK, M.D., BROOKLINE, MASS.

(From the Free Hospital for Women)

PHYSICIANS and laymen have long thought that it is quite common for couples who have previously been childless to have a child of their own following adoption. Many people can cite one or more cases they know of personally, and when asked will preface their statement with a remark that the phenomenon is well known. Yet we find no report of an accurate survey of how often this sequence occurs nor, assuming its frequency, of what is its etiology. The theory grows among physicians that psychogenic disturbances play an important part in reproductive physiology and may influence conception. Proponents of this theory assert that adoption relieves the inhibiting psychogenic factor and allows the conception. A limited survey of the possible occurrence of this relationship and of what effect adoption may have on other related reproductive functions has been made and is reported in this paper.

The literature contains little that is directly concerned with the cause of these possible phenomena, although several papers have definite bearing upon the subject. None has given any percentage of frequency of occurrence. In 1936 Perkins¹ reported a study made over a five-year period in which he approached people through the medium of a magazine article asking for voluntary responses to his questionnaire. Two hundred seventy-three people reported that having adopted a child they subsequently had normal pregnancies, ranging from one to fifteen children. No percentage of frequency can be calculated from this study since no one reported adoption without subsequent pregnancy, although the stated purpose of the author was to find "whether infertility is ever or often affected by the decision to adopt." He discusses as provocative decisive factors bringing about the infertility, excessive mental strain, worry over financial matters, guilt feelings due to puritanical upbringing, or perhaps subconscious guilt feelings because of past indiscretions. Thus, in this early study of the problem itself, a psychiatric basis is proposed and discussed. Perkins postulated that perhaps "an imbalance of endocrine influence may be balanced by adoption whereas just the desire to adopt is not sufficient." Actual adoption then is the particular factor, according to him, which permits conception and parturition.

Dunbar² in 1938 summarized the work of Sellheim,¹² Mohr,¹³ and A. Mayer¹⁴ done between 1925 and 1930, and stated, without acceptable proof, that "psychic influences associated with a vivid but unsatisfied desire for a child, may stimulate the ovaries to pathological growth. It is possible that this may result in premature maturation of the follicles and discharge of the ova which are not yet ready for fertilization, and consequent sterility. That there are peculiar cases of first conception after 15-20 years of married life may be explained by the fact that as a woman gradually becomes reconciled to her sterility this injurious influence on the follicular apparatus disappears."

Orr³ in 1941 reported a case of "Pregnancy Following the Decision to Adopt," which he attributed in large part to psychosomatic causes. Both members of the couple had had over 500 hours of psychoanalysis which

brought out evidences in each member of conflicts dealing with repudiation of femininity and masculinity. Their decision to adopt was followed immediately by a normal conception, which ended in normal delivery, the last menstrual period occurring eleven days following the time the application to adopt was made. The baby was chosen fifteen days after the onset of menstruation and the wife had no further periods. The pregnancy followed a period of ten years of infertility, seven of which were because of controlled conception. Prior to the decision to adopt, a period of three years of infertility without contraception passed, during which pregnancy was desired and attempted. It must be stated, however, that associated in this case is a history of pelvic endometriosis for which the wife was treated surgically 13 months prior to the normal conception, at which time a Fallopian tube and ovary were removed. There are many cases of infertile patients with pelvic endometriosis, however, who, by surgical treatment, have been enabled to conceive, usually within two years following surgery. This must be remembered as a possible cause of the conception in this case, adoption then only incidental. Here, again, however, a psychosomatic cause of infertility is proposed.

We quote at length from Knight⁴ (1941). "We are all aware of the frequency of 'conscious' opposition to having children in married couples, so that they take extreme precautions to avoid conception. This conscious opposition is attributed to the conviction that they cannot afford children, that they do not want to have their social life and freedom from responsibility interfered with, or so on—in such couples it may happen that after some years they decide to have a child and then find that they cannot bring about conception. The conscious opposition has been changed by considerations such as the realization of the barrenness of their childless home or a growing feeling that the marriage is nearing the rocks and a child is needed to bind them together again. The unconscious opposition, however, has not changed and still operates to prevent pregnancy. It is obvious that a couple who have recently changed their attitude in regard to having children are thus open to the suspicion that the strong opposition still lingers, and this opposition may be manifested by their prolonged indecision as to just when they will carry out the adoption or by excessively rigid specifications which a prospective adopted child must meet in order to be acceptable to them." Here is proposed the basic question in a study of the effect of adoption on fertility: can a psychogenic factor, of itself, cause the infertility that exists before adoption and disappears afterward? Knight accepts such a relationship and describes how he thinks the effective cause is made manifest.

William Menninger⁵ states that probably the most prominent factor in psychogenic sterility is fear of the inability to become pregnant. He lists three cases in his own personal experience which he proposes as cases of psychogenic infertility relieved by adoption, and lists as well, in verification, Orr's case (previously discussed) stating it to be a similar case, making no mention, however, in his résumé of the case history, of the pre-existence of the endometriosis. Robbins⁶ in 1943 reiterated the possible underlying psychogenic conflicts which bring about infertility and stated that "a promising opening for psychologically oriented investigation of problems relative to conception is the well-known phenomenon of conception in a previously sterile woman after she has adopted a child. Unfortunately, accurate statistics of the frequency of such events are not available but inasmuch as almost everyone knows of one or two such incidents they must occur frequently." We feel, however, that perhaps those cases that do occur are so well publicized that the relative frequency of the occurrence is in turn overemphasized. Weiss⁷ discusses these factors as well.

Karl Menninger⁸ states also (1942) that the unconscious wish not to have a child may exist even though conscious appearances deny it, and claims the disturbance may be due to a repudiation of femininity, but more frequently is based on a tremendous unrecognized fear. Further he states that "we should logically expect that the significant alterations in functions or structure related to the repudiation of femininity would be connected with the reproductive organs. Frigidity and vaginismus represent physiological rejections of the feminine role in intercourse and cannot exist over a long period without some corresponding structural changes, such as (at least) the atrophy of unused tissues and glands." This last statement may be seriously questioned. Disuse has not been shown of itself to cause atrophy of the vaginal tissues or any of the reproductive organs or glands. He states further, however, "sterility is somewhat comparable to frigidity: it represents the failure of normal biological functioning. That it occurs far oftener among human beings than among animals, should have suggested before now that something in the spirit of our civilization interferes with a process generally regarded as beyond psychological control." He mentions also the reported cases of "reorganization of the psychic life (e.g. psychoanalysis) of a woman resulting in pregnancy 10, 15, and 20 years after marriage," and that "moreover, pregnancy frequently follows the adoption of a child." Evidently he feels that this is a very common occurrence, since he writes that "such phenomena as the occurrence of pregnancy following the adoption or decision to adopt a child are frequent enough to belie the explanation of coincidence for even the most organically minded doctors." Statistical evidence of sufficient frequency to "believe the explanation of coincidence" is not given. In his book, *Love Against Hate*,⁸ he offers the following statement as possible verification of the existence of psychologic control over reproductive functions as evidenced in the animal world.

"Every ornithologist is familiar with the phenomenon observable in the woodpecker family and in some other birds: if a normal clutch of eggs is, let us say, six, the artificial removal or loss of one of the eggs will result in another being laid to replace it, and this can be repeated many times. It is clear that the female has some psychological control over the number of eggs she produces, the stimulus of the awareness of a certain 'perfect' number."

We are permitted to quote in total a letter received from Ludlow Griscom, Research Ornithologist at Harvard College, in response to our question about this phenomenon in the woodpecker family and in bird life in general.

"Karl Menninger's statement in his book is an amusing combination of half truths made into glittering generalizations. The ascertained facts would appear to be approximately as follows:

"(1) The great biological mystery about most birds is roughly this: The ovaries manufacture a large number of eggs, but only the number needed to constitute the normal clutch are matured, ripened, and laid. What prevents the development of other eggs and how they are absorbed into the system is entirely unknown. Moreover, in the great majority of birds on earth the normal clutch is far more than three, and as experiment fails to show that any bird can count beyond three, there can be no 'awareness of a certain perfect number,' to quote Menninger.

"(2) Menninger's facts about the woodpecker family are incorrect and distorted. Many decades ago somebody experimented with a female flicker and made the remarkable discovery that if two eggs were laid and one was taken, leaving one, that particular female flicker laid seventy-one in seventy-three days. This experiment has been repeated on four subsequent occasions with four other female flickers. No two of these individuals proved alike, and none

of the four laid more than forty eggs. It should be clear that experimenting with five different female flickers does not warrant a generalization about the woodpecker family, which contains at least two hundred species.

"(3) All experiments agree perfectly that if the normal clutch of eggs is, let us say six, and one egg is taken, no known bird on earth is aware of the loss of the egg.

"(4) The experiment performed on the five flickers, mentioned above, would be fruitless in the great majority of birds because they desert the nest when discovered, if only one or two eggs have been laid. The reference to the experiments on the flickers is Bales: *Wils. Bull.*, 1917, pp. 188-191."

In the literature thus far quoted we find no definite proof of a psychogenic influence on reproductive functions, and feel that those instances of possible examples are only speculative in nature.

Helene Deutsch⁹ discusses the role of psychogenic factors in the production of sterility and gives an excellent account of conflict patterns and personality types which one encounters in the psychoanalytic study of these patients. She states, however, that "every form of psychogenic sterility is only relative—that is to say, it can be eliminated if the psychic conditions are changed (provided the organic situation permits), and that the same psychic factors may manifest themselves only in later phases of the reproductive function without disturbing its first phase, fecundation." She continues, "in general it can be said that the most frequent cause of (psychogenic) sterility is unconscious fear. This fear may relate not only to the reproductive function, but to everything sexual, thus eliminating any possibility of physical motherhood by exclusion of the sexual experience." Yet, "seen as a functional disorder, psychogenic sterility in woman is a very complicated and stubborn phenomenon; its initial cause is usually difficult to discover, even though modern methods of investigation can find the disturbances in the hormonal messenger service. Yet, strikingly enough, the symptom (sterility) frequently persists despite favorable treatment of the hormonal defect, because, in our opinion, it continues to be fed by psychic energies."

That psychogenic factors may play an important part in other aspects of endocrine dysfunction, than failure of conception, also is possibly true. That frequent anovulation with or without amenorrhea affects fertility is self-evident. Benedek and Rubenstein¹⁰ have studied and summarized the correlation between psychodynamic processes and ovarian activity in general. Ripley and Papanicolaou¹¹ studied how frequently menstrual disorders are encountered in the various psychoses and found a high percentage. Many cases of amenorrhea following nervous strain or fatigue are reported. Especially during World War II this was found to occur in the wives of military men during periods of great anxiety.

Thus one may for the moment accept the prevalent opinion that there exists a definite connection between psychogenic factors and endocrine dysfunction in the woman. But how the effect of psychogenic factors is mediated is yet a matter of speculation. We believe that the equally prevalent opinion that adoption may relieve infertility is questionable.

Description of Study

Methodology.—Through the aid of adoption agencies a study was made of 202 couples who adopted, approximately between 1938 and 1948. The cases of adoption in the six to twelve months immediately preceding the survey were not included as it was felt that sufficient time had not elapsed since adoption to make evident its possible effect on fertility. The couples were approached by means of a questionnaire asking whether or not they had had children following adoption, and other pertinent information. Advantage was also

TABLE I

CASES	PREG- NANCIES BEFORE ADOPTION	YEARS OF INFERTILITY BEFORE ADOPTION	EXPOSURE YEARS BEFORE ADOPTION	TIME LAPSE BETWEEN ADOPTION AND PARTURITION	CONTRACEPTIVE PRACTICES	OPERATIONS PRE- AND POST- ADOPTION	STERILITY SURVEYS BEFORE ADOPTION	FURTHER STUDY AFTER ADOPTION	CAUSE OF PRESUMED INFERTILITY
A.	0	7	5	2 years 4 months	Douches and con- dom 1 year	Cauterization of cervix, preadop- tion	Very complete	Yes, donor in- semination	Oligospermia
B.	4 aborted	2	2	3 years	None	None	None	Yes	None
C.	1 aborted	13	12	2 years 5 months	None	None	Complete	None	None
D.	0	4	3	3 years 3 months	None	Uterine suspen- sion, preadoption	Complete	Yes	Tubal occlusion
E.	0	9	6	3 years	Rhythm one year, diaphragm, two years	None	Partial	None	None
F.	0	13	11	9 months	Diaphragm two years	Oophorocystec- tomy, preadop- tion	Partial	None	None
G.	0	7	4	13 months	Diaphragm three years	None	Very complete	None	Juvenile uterus, anovulation
H.	2 aborted	4	3	4 years	None	None	None	None	"Internal weak- ness"
I.	1 aborted	6	5	3 years 3 months	Diaphragm one year	None	Complete	None	Oligospermia
J.	0	4	3	2 children 14 months, 26 months	Withdrawal one year	None	Complete	None	None
K.	1 aborted	6	4	17 months	Diaphragm and douches, two years	None	Complete	None	Oligospermia

taken of the opportunity to discover what we could on the possible influence of adoption on some other aspects of reproductive physiology. Eighty-five of the 202 were studied by a more detailed questionnaire as to the etiology of their infertility. Of these eighty-five couples, eighteen wives were within the age group 20 to 29 years, sixty-three within the thirties, and four within the forties, with a high of 44 years.

TABLE II

CASES	REASONS GIVEN BY ADOPTIVE COUPLES AS TO CAUSE OF THEIR PREGNANCIES FOLLOWING ADOPTION	
A.	Further infertility study and treatment after adoption (donor insemination)	
B.	None	
C.	"Greatly increased love, understanding, and appreciation of children since having them in our home."	
D.	None	
E.	None	
F.	"Release of mental strain. Prior to adoption, outside activities had exhausted me [wife] mentally, was extremely run down."	
G.	"Tension of wanting baby relieved by adoption—only matter then of producing one of our own, once we had adopted and producing one no longer in our minds."	
H.	None	
I.	None	
J.	"We were very happy and probably more contented. I think that anxiety has a lot of influence in this matter. We have now had two normal children since adoption."	
K.	"Complete relaxation from the tensions caused by our great desire for a child."	

Results.—Pregnancies were reported in fifteen cases out of 202. Eleven of these fifteen were studied as to the cause of the presumed infertility and how it was relieved. The result is given in Table I and discussed later. Table II includes those reasons given by the involved couples as to the cause of their pregnancies.

Of the 85 cases studied (including the aforementioned eleven cases from among those in whom pregnancy followed adoption), the following facts are of value. Seventy-four adopted because of childlessness alone, two because of a limited number of natural children already in the home, four because of neonatal deaths, three because conception was avoided due to the existence of constitutional disease in the wife, either renal or cardiac, which contraindicated pregnancy, and one because of psychologic disturbance diagnosed before fertility had been tested. Thirty-five of the 85 couples reported pregnancies prior to adoption that failed to reach term. Sixty-five had had sterility surveys of varying completeness. Fifty-one of these sixty-five knew of apparent causes for their sterility. Table III lists these causes.

Forty-five of the 85 submitted to operations in treatment of their infertility or of existing pathology. These included the common operative procedures such as tuboplasty, myomectomy, dilatation and curettage, uterine suspension, and oophorecystectomy. Contraceptive practices included all of the usual devices, the vaginal diaphragm being used in most instances, though only for a relatively short period of time. As evidenced most couples adopted well within the reproductive ages. Occupation seemed to have no effect on fertility in any instance.

Following adoption, nineteen of the 85 couples reported changes in menstruation, the most common change being loss of premenstrual and menstrual discomfort. The next most common change was in the length of the cycle, with two reporting change in the amount of flow during menses. One reported more regularity of menses of a twenty-eight-day type with slight pelvic pain and

midmenstrual spotting on the fourteenth day, possibly denoting in this patient a beginning of ovulation, or at least, more regularity of ovulation. Twenty-two couples reported sexuality changes, mostly on the wife's part, the majority reporting less tension with intercourse, more ease of act, and more enjoyment. Two reported less interest in intercourse, due to, as they describe, cessation of interest in having natural pregnancies. The remainder of the 85 reported "no change" in both menstruation and sexuality, which is of no value in interpretation.

TABLE III. CAUSES OF STERILITY

A. Male		C. Those with unknown causes of sterility		23
1. Oligospermia, due to mumps orchitis	2	D. Constitutional diseases found in		
2. Oligospermia, unknown etiology	14	Male		6
3. Azoospermia, unknown etiology	2	Female		39
4. Azoospermia, due to x-ray to testicles	1	including:		
B. Female		1. Hypothyroidism		
1. Anovulation	7	2. Cardiac pathology		
2. Tubal occlusion	6	3. Renal pathology		
3. Tubal absence	6	4. Tuberculosis		
4. Habitual abortion	6	5. Congenital hypoplasia of genital organs		
5. Juvenile uteri	6			
6. Absence of uterus and ovaries, operative	6			
7. Rh deaths of child	1			
8. Hereditary, in all sisters of family	1			

Discussion

Is adoption frequently followed by pregnancy? Fifteen, or 8 per cent, of the 202 adoptive parents achieved a subsequent pregnancy. This figure of 8 per cent is not remarkable compared to statistical surveys in general, since ten per cent of spontaneous cures are to be expected. Therefore, we can say adoption is not followed by normal pregnancy to any remarkable degree.

One may ask, however: Can adoption in any of these fifteen be considered as effecting the subsequent pregnancy? Unfortunately we know details of sterility in only the 85 cases previously mentioned as having returned comprehensive questionnaires. Eleven of the fifteen pregnancies fall within these 85. Let us eliminate from the 85, six cases of bilateral salpingectomy, six of pan-hysterectomy, and three of azoospermia, a total of fifteen. Of the remaining seventy couples with potential fertility, eleven, or 15.7 per cent, reproduced.

It is instructive to consider the available information in these eleven (Table I). Five couples had uncompleted pregnancies prior to adoption. In two of these five there was oligospermia. There exists the very strong possibility that the pregnancies following adoption in these two cases were a matter of chance, not uncommonly encountered in oligospermia. The other three cases could possibly be explained on a similar basis. Whether or not psychogenic disturbances played a part is speculative. Possibly the adoption acting as a cure for psychogenic disturbances allowed in some way a pregnancy to be carried to term. We feel that even less possibly adoption acting again in the same way may have eliminated whatever disturbances existed which caused the oligospermia. Certainly, we have very little if any proof for these speculations. Spontaneous cures in habitual abortion and oligospermia without adoption are not rare. We feel that the burden of proof lies with psychogenic disturbances, since in these five cases adoption is not clearly the curative factor.

One of the cases of infertility in this group was reportedly due to a juvenile uterus and anovulation. Here, again, we feel that chance plays a part since perhaps ovulation had always been infrequent and only now after a short four-year exposure period was conception possible regardless of adoption. We could speculate again in this case that adoption in some way was responsible for more regular ovulation. It seems that there are many proponents of this theory from the literature reviewed here. We think the theory may be right, but we cannot prove it.

The history most clearly suggesting a psychogenic factor involved in pregnancy following adoption would be one in which a long period of infertility existed even though the husband and wife had been shown by present examination methods to have no defects, and in whom adoption was followed very shortly by a normal pregnancy. Only one of the eleven cases conforms to this ideal, Case F in Table I, in which eleven years of infertility were followed nine months after adoption by a normal delivery, indicating, as in Orr's case, that the conception occurred at the time of adoption. This strongly suggests an underlying psychogenic disturbance relieved by adoption, although what the physiologic counteraction was, is impossible to determine. This case also contains a history of an oophorectomy. What part this played in the conception is also difficult to determine, especially since we do not know when the operation was performed in relation to the adoption.

Three other couples showed a similar history of pregnancy occurring relatively soon after adoption but with a shorter exposure time than in the case above. It is interesting to note that each of these four cases described above (Cases F, G, J, and K in Tables I and II) in which possibly a psychogenic factor existed attributed their normal pregnancy to the adoption, which acted, as they describe, by relief of mental strain connected with childlessness.

It should be mentioned that in one of these eleven cases we have proof that donor insemination was responsible for the pregnancy. In such an event, of course, this case should be excluded from the group.

What evidence have we that adoption affects other reproductive functions? We have mentioned previously that twenty-two couples out of 85, studied in detail, reported sexuality changes, mostly on the wife's part, and nineteen reported menstrual changes. The most commonly reported effects on sexuality were less tension and more enjoyment during intercourse and more ease of act (perhaps denoting less pain in intercourse). Two reported less interest in intercourse, for reasons previously given. These changes all seem easily explainable on a better psychologic outlook following adoption. The most common menstrual change reported by nineteen couples of the 85, loss of menstrual discomfort, also could be explained on the same psychological basis. Of the eleven cases in which pregnancy followed adoption, only two were reported as having had changes in sexuality described above. In only one case pregnancy followed a marked improvement in menstruation.

Therefore, we feel that no correlation can be made with improvement of either menstruation or sexuality that might be considered effective in bringing about conception. No greater percentage of changes was reported in the group in which no pregnancy followed adoption than in the other group. There seems, in fact, to be no significant physiologic factors on which this phenomenon could be explained. All this then perhaps suggests an underlying undetected factor which possibly may have some bearing in psychosomatic activity. We have pointed out also four cases of pregnancy following adoption in which psychogenic factors may have played a part judging from the evidence given. Most of the menstrual and sexuality changes reported, of course, are psychological by definition.

Summary and Conclusions

The literature affirming the therapeutic effect of adoption on infertility is quoted and discussed. It is all speculative and without proof.

A survey of 202 adoptive couples revealed subsequent pregnancy occurring in fifteen (8 per cent). Spontaneous cures of infertility without adoption are generally considered likely in 10 per cent.

A more detailed study of 85 of the 202 couples was made. In fifteen of these the wife had been sterilized or the husband azoospermic. Eleven of the fifteen pregnancies, or 15.7 per cent, fell in the remaining group of seventy cases. One followed donor insemination because of oligospermia. There was oligospermia in two other cases. Isolated or widely separated pregnancies are not uncommonly achieved by men with exceedingly low sperm concentration. In two cases with oligospermia and in three others there had been abortions previous to adoption. Malpas¹⁵ reported successful delivery after three abortions as occurring in 27 per cent of such cases, and in 62 per cent after two abortions. Eastman¹⁶ calculated successful delivery in 16.4 per cent of cases with three previous abortions, and a similar figure to that of Malpas in cases with two abortions. In these five instances then adoption seems not to be the definitive curative factor.

Of the remaining five cases, in one there had been previous anovulation. That adoption relieved this condition is purely speculative, for spontaneous inexplicable ovulation often occurs in the habitually anovulatory female.

In the residual four cases, adoption was followed by improvement in the wife of the emotional tone, and there is no other explanation for cure of infertility. These pregnancies also were conceived very closely following adoption. As these contribute only 7 per cent of the seventy cases of potential fecundity, we believe they do not prove that adoption is a likely cure for sterility.

Of 85 women, twenty-two (26.2 per cent) reported improvement in sexuality, and nineteen (22.6 per cent), more normal menstruation following adoption. The causal relationship is problematical.

The authors gratefully acknowledge the invaluable aid given in this research project by Miss Madeleine Hoagland of the Children's Friend Society of Boston and Miss Constance Rathbun of the Children's Aid Society of Boston.

This study was aided by a grant from the Committee on Human Reproduction of the National Research Council.

References

1. Perkins, H. E.: *Eugenical News* 21: 95, 1936.
2. Dunbar, H. F.: *Emotions and Bodily Changes*, ed. 2, New York, 1938, Columbia University Press.
3. Orr, D. W.: *Psychosom. Med.* 3: 441, 1941.
4. Knight, R. P.: *Bull. Menninger Clin.* 5: 6, 1941.
5. Menninger, W.: *Bull. Menninger Clin.* 7: 15, 1943.
6. Robbins, L. L.: *Bull. Menninger Clin.* 7: 41, 1943.
7. Weiss, E.: *Human Fertil.* 10: 74, 1945.
8. Menninger, K.: *Love Against Hate*, ed. 1, New York, 1942, Harcourt, Brace, and Company, Chap. 4, pp. 95-97.

9. Deutsch, H.: *Psychology of Women*, ed. 1, New York, 1944, Grune and Stratton, Inc., Chap. 5.
10. Benedek, T., and Rubenstein, B. B.: *Psychosom. Med.* 1: 245, 1939.
Benedek, T., and Rubenstein, B. B.: *Psychosom. Med.* 1: 461, 1939.
11. Ripley, H. S., and Papanicolaou, G. N.: *Am. J. Psychiat.* 98: 567, 1942.
12. Sellheim, H.: *Gemütsverstimungen der Frau. Eine Medizinisch-juristische Studie*, Stuttgart, 1930, Ferdinand Enke.
13. Mohr, F.: *Psycho-physische Behandlungsmethoden*, Leipzig, 1925, S. Hirzel.
14. Mayer, A.: *Psychogen Störungen der Weiblichen Sexualfunktion*. In: Schwarz, O.: *Psychogenese und Psychotherapie Körperliche Symptome*, Wien, 1925, Julius Springer.
15. Malpas, P.: *J. Obst. & Gynaec. Brit. Emp.* 45: 932, 1938.
16. Eastman, N. J.: *Habitual Abortion*, In *Progress in Gynecology*, edited by J. V. Meigs and S. H. Sturgis, New York, 1946, Grune and Stratton, Inc., pp. 262-268.

Nizza, M.: On the Ogino-Knaus Theory, *Ginecologia* 14: 92, 1948.

The author reviews the Ogino-Knaus theory which fixes the period of ovulation between 16 and 12 days preceding the next menstrual period. Since the viability of the spermatozoa is three days, the relative fertility of the female is placed between 16 and 9 days before the next period.

Several authors are cited who attempt to invalidate the Ogino-Knaus theory with reference to conceptions that have occurred out of the range of fertility as specified by Ogino and Knaus. One mechanism is supposed to be the release of the ovum in a nearly mature Graafian follicle following certain emotional factors. The present author attempts to discount these references after reviewing the menstrual cycle of several women and realizing that, in the event of conception outside the physiological range of fertility, there was a miscalculation. When shorter than twenty-eight day cycles were considered, the day of ovulation still fell within the period specified by Ogino-Knaus. The constancy of the ovulatory date must be based on its relationship to the beginning of the subsequent menses. Relative to the previous period there is no fixed relationship.

In other words, in general, the luteal phase lasts from 16 to 12 days, whereas the duration of the proliferative phase is peculiar to the length of the cycle itself. Thus the author correlates his conclusion with adequate basal temperature and also with the Farris method for determining the time of ovulation.

FRANK A. GRACEFFO.

EMOTIONAL FACTORS IN GYNECOLOGY

FLOYD S. ROGERS, M.D., WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, The George Washington University School of Medicine)

OF ALL the medical specialties, there is perhaps none so closely allied to psychiatry as gynecology. Probably half of all patients who present themselves for treatment have no gross gynecological pathology.

Psychoanalytic experience has revealed that disorders in gynecologic functions are often the result of emotional conflicts which are involved in the mechanisms of the unconscious. Therefore, in those cases where such conflicts are present, psychotherapy is an absolute requirement for successful treatment. Accordingly, there is a definite need for some understanding of the mental processes of individuals seeking gynecologic care, if their symptoms are to be properly evaluated.

It is well known that the hormonal function of the endocrine system is dependent upon the type of coordination which exists between the central and peripheral nervous systems. Emotional irritations communicated through the sympathetic and parasympathetic nervous systems often disturb the endocrine balance which results in functional gynecological disorders.

Since the time of Hippocrates and Galen, and until as recently as the turn of the century, physicians attributed hysterical disturbances to diseased genital organs. The unwillingness of the gynecologist to concern himself with the problem of primary psychogenic genital disturbances undoubtedly can be identified with the academic or scholastic emphasis placed on bacteriology, pathology, and the development of operative technique. Walthard¹ states that Kroenig should receive credit for stressing, as early as 1902, the importance of functional nervous disorders in gynecological diagnosis and therapy. Kroenig emphasized the frequent occurrence of psychogenic pruritus vulvae and mentioned the psychogenic sensation of prolapsus uteri when there was no anatomical evidence of prolapse of this organ. It was not until many years later, in 1919, that Graefe² reported similar observations. The majority of gynecologists did not agree with Kroenig that disturbances might be caused solely by a psychic process; they suspected rather that disturbances resulted from somatic changes in either the central or peripheral nervous system. Walthard,³ in his Frankfurt clinic, was the first to separate patients with psychogenic disturbances from those with organic disease; and to insist that the former be treated psychotherapeutically.

Allbutt,⁴ in 1884, in his lectures on Visceral Neurosis, made the following statement: "A neuralgic woman seems thus to be peculiarly unfortunate. However bitter and repeated may be her visceral neuralgias, she is either told she is hysterical or that it is all uterus. In the first place she is comparatively fortunate, for she is only slighted; in the second case she is entangled in the net of the gynecologist, who finds the uterus, like her nose, is a little on one side, or again like that organ, is running a little, or it is as flabby as her biceps, so that the unhappy viscus is impaled upon a stem, or perched upon a prop, or is

painted with carbolic acid every week in the year except during the long vacation when the gynecologist is grouse shooting, or salmon catching, or leading the fashion in the Upper Engadine. Her mind thus fastened to a more or less nasty mystery becomes newly apprehensive and physically introspective and the morbid chains are riveted more strongly than ever. Arraign the uterus, and you fix in the woman the arrow of hypochondria, it may be for life."

If anyone thinks that this attitude has changed, let him be disillusioned. Menninger⁵ says that the majority of female psychoneurotic invalids by whom psychiatrists are consulted have had gynecological treatment if not gynecological surgery. Too much gynecological treatment is being given and too little etiological thinking is being done. Many patients present gynecological symptoms without being sick gynecologically. Their illness represents a psychic conflict sailing under a gynecological flag, a fact which has not escaped the attention of the unscrupulous.

Menstruation

Menstruation and its far-reaching psychological effects have been well covered in a monograph by Chadwick.⁶ From the earliest times, the menstrual period in women has been surrounded with the idea of horror and guilt, leading to strict taboos and an endless number of strange superstitions, many of which survive to the present day. Many centuries of education and enlightenment are necessary if we individuals are to be rid of many of these old beliefs and superstitions, because as we know, such beliefs die slowly. The girl of today, though better informed than the girl of a few decades ago, is nevertheless subjected to certain restrictions during menstruation and she is instilled with many superstitions regarding the menstrual function. Fear and anxiety are common in women during menstruation and they frequently refer to themselves as "being ill." They fear to take baths and believe themselves dirty and disgusting to men. As the result of teaching by their mothers or others, many women prefer to remain in bed for a day or two lest the bleeding become too profuse or stop completely if they go about their work in the usual manner. In primitive tribes, menstruation was regarded as a sign of sexual excitement. In later stages of society, the sexually excitable woman was regarded as a danger to the stability of the home, and to the legitimacy of the heir. Although these misbeliefs have since been dispelled, there persist various taboos regarding menstruation itself. It is a known fact that increased sexual excitement around the time of the menstrual period occurs in many modern women. Many people of both sexes regard menstruation as unpleasant or dirty because they associate the menstrual flow with an unpleasant excretion which cannot be controlled. Some women regard menstruation with anxiety because it stirs up some childhood fantasy of an injury. Some women regard menstruation to be a repeated confirmation each month of a belief that they have injured themselves through masturbation.

The effect on her children of the indisposition of the mother during menstruation is important. At this time she may be irritable, depressed, and possibly remain in bed. The child may become aware that bleeding is taking place, without being given any explanation of the cause, and the young mind logically turns to ideas of injury, pain, and fear of genital mutilation.

The young girl, at the onset of menstruation, often enters this new experience unenlightened by her mother, as a result of which she feels unclean, unpopular, and unwanted by her family or society in general. Unfortunately, she is also told that her activities and pleasures have to be curtailed at this time. It is not surprising therefore that, with these misconceptions conceived during puberty as well as those which may be conceived during adolescence, women grow morose and irritable as their menses approach each month. A problem is also presented by the girl who, as a child, envied the attributes of the male and who

then has her hopes of growing into masculinity blasted with the onset of menstruation. She regards her bleeding as proof positive of her commitment to the feminine role and if this role has not been presented to her as normal and desirable, her frustration may have a saddening, if not traumatic, effect.

It is also a fact that many girls approach puberty with the expectation that with menstruation they will be accepted by their mothers, sisters, and other women on a more intimate basis. However, since women generally regard menstruation with little dignity, such girls find themselves with all the discomforts of menstruation and with none of the anticipated advantages of maturity. Thus, menstruation may stir up fantasies of hostility toward both sexes: hostility toward men because of envy of the freedom to which their organs appear to entitle them; and hostility toward women because of her mother's responsibility for bearing a child of that sex.

Disturbances of menstruation are daily problems confronting the gynecologist and the importance of psychic factors is generally known but little appreciated. All effects can accelerate or retard it. Menninger contends that disturbances of menstruation may be directly associated with an unconscious repudiation of femininity. Of these disturbances amenorrhea is, therefore, the most logical; dysmenorrhea probably the most frequent. Menorrhagia, metrorrhagia have also been identified as psychological and, by correction of psychopathology, cured. Cessation of menstruation may occur through fear and apprehensiveness concerning the possibility of pregnancy; on the other hand, it may at times be noted in the case of nonpregnant women intensely eager for motherhood.

Case Reports (Amenorrhea).—

1. A patient, aged 25 years, was referred by a gynecologist in another city. Her complaint was amenorrhea of eight months' duration; her menses prior to this had been normal. A physical examination by her former physician had failed to reveal any abnormalities. Her basal metabolic rate was minus twenty-five and three grains of thyroid were prescribed daily, which changed it to plus two. This amount was continued for three months, from the third to the sixth month of amenorrhea, without the return of menstruation.

When the patient was first seen the only abnormal finding was a basal metabolic rate of minus twenty-two. While giving her history, she was asked if anything unusual had happened eight months ago, just previous to onset of amenorrhea. She stated that she had been divorced from her husband after four years of marriage and had remarried immediately thereafter. Her family thought the divorcee was unwise and had sided with her former husband in the disagreement. Consequently, she was ostracized by her family, felt very guilty, and was eager to discuss her troubles. She was advised to re-establish her family relations on a more congenial basis. Twenty-two days from the time of her first visit she had a normal period, and after menstruating normally for five months, she became pregnant.

2. A patient, 19 years of age, was brought by her mother, with a complaint of amenorrhea of three months' duration. This girl was not married but, allegedly, had sexual intercourse once approximately three and one-half months before.

Physical examination revealed no abnormalities. The hymen was intact. Rectal examination revealed a normal uterus and adnexa.

She was not pregnant. A Friedman test was suggested. This was done, but forty-eight hours after she was told she was not pregnant and before we got the report from the laboratory, she had a normal period.

Functional Uterine Bleeding

Functional uterine bleeding is frequently psychological in origin. The disturbances in the endocrine system may be due to hypofunction or hyperfunction. Gynecologists have been content to study the function of the glands

and have tried to supply the deficiency or reduce hyperactivity. While there are many factors in endocrine imbalance, changes from normal may be induced primarily by some exciting or inhibiting influence emanating from the psychic. The amenorrhagia which results is a manifestation of the psychic disturbance.

Novak and Harnik⁸ reported forty-five cases of psychogenic uterine bleeding. In all cases but one it was possible to elicit a psychic trauma leading to the bleeding. In many of these cases, patients had been treated unsuccessfully with medication for months or years but most of them were cured by psychotherapy.

Case Reports.—

1. A patient, aged 32 years, complained of menometrorrhagia following the birth of her third child, eight months before. A physical examination failed to reveal any abnormalities. During discussion reference was made to the annoyance and inconvenience caused by her bleeding. She stated that she had been worried about her condition, but this concern was counterbalanced by her fear of another pregnancy. Since her last confinement she had had no desire for coitus, and, since this was precluded by her bleeding, she had delayed seeking medical advice.

After further discussion, it was learned that her pregnancies had occurred despite the use of a diaphragm and creme and consequently she had no confidence in this method of contraception. Her husband was interviewed. It was suggested that he use a condom, which he did successfully. After the basic fear of pregnancy was removed through the use of this contraceptive method, the patient began menstruating normally and has continued to do so.

2. A patient, 28 years of age, was first seen because of menometrorrhagia, of thirteen months' duration. Her menses had always been perfectly normal until the onset of her chief complaint. Physical examination failed to suggest any cause for her bleeding other than functional. During the course of our discussion she said that during the past year her marital relations had not been good and that three months ago her husband had asked for a divorce so that he could marry someone else. Out of spite she had decided not to give him a divorce even though they were separated.

She was advised that she had nothing to gain by her attitude and that her symptoms would not improve as long as she lived under such tension. Finally she consented to the divorce and shortly thereafter her menses became regular and have remained so.

Dysmenorrhea

Dysmenorrhea is one of the most common symptoms of gynecologic disorders. Painful menstruation secondary to pelvic pathology has an obvious cause and one's attention is focused on the treatment of that disease. However, primary dysmenorrhea, without pelvic pathology, has been a subject of extensive discussion for hundreds of years. It is still an unsolved problem.

Functional dysmenorrhea is a symptom complex associated with menstruation which affects, in addition to the pelvic organs, the personality as a whole. All symptoms are closely interrelated and each supports and perpetuates the other.

"Personality Studies in Dysmenorrhea and Sterility," by Wittkower and Wilson,⁹ strongly suggests that dysmenorrhea predominately occurs in individuals with certain psychological characteristics which antedated the onset of their complaint. As children they showed psychological maladjustment four times as often as the control group. As adults the patients with dysmenorrhea showed a high excess of two main personality groups. The first was characterized by deep resentment of their feminine role; the second was obviously immature physically and either shy and shut in or chronically anxious and complaining.

One naturally asks: What are the dynamics by which the symptoms of

dysmenorrhea are produced? Psychological attitudes and allied emotional states may lead to increased interest in and awareness of physiological uterine function or to an autonomic endocrine disturbance affecting uterine function, or to both. In the second place, as elsewhere, the pain might easily arise from relative ischemia through disturbances of the relation between the reciprocally innervated muscular contraction of the corpus and cervix uteri and the vasomotor state of the organ.

Lewis,¹⁰ who has spent a lifetime in the study of pain, says, "Pain cannot be defined; it is something we learn from experience and describe by illustration." The function of the sensory nervous system is to acquaint the conscious mind with the nature of the external and internal environment in order to regulate autonomic processes and coordinate muscular movements. Also, it should be remembered that cortical cells have the function of spontaneous activity, and that pain can appear spontaneously through association with some previous painful experience. Once impulses are recognized as painful, they become associated with previous environment. Repetition tends to strengthen these connections so that the mosaic patterns of excitation or inhibitions are created in the cerebral cortex—patterns which profoundly alter the bodily reactions. Some persons so strongly identify events with painful experiences that every time they subsequently encounter a like event a painful reaction is felt. Therefore, it is easy to believe that symptoms may occur when one realizes that menstruation is being associated with certain old events, experiences, and queer ideas. In her dysmenorrhea, a woman is reminded of some situation of her past, and, at the same time, is prevented from realizing this situation. This explanation is based on the concept of the unconscious which makes simple, logical explanation of the dependence ineffective to the sufferer. For that reason, a neurotic is never capable of correcting her misconceptions by experience. The origin of dysmenorrhea is the neurotic belief that menstruation, a phenomenon of so great an importance and impact, must afflict the sphere of feeling. Anxieties and fears are experienced because some repressed material is touched upon; the neurotic associates anxiety with menstruation, thus establishing an organ neurosis.

Case Reports.—

1. A patient, aged 21 years, reported because of incapacitating dysmenorrhea of four months' duration. The time of menarche was age 13 and she had had slight cramps on her first day of menstruation. Since arriving in Washington from a small midwestern town four months before, her cramps, accompanied by nausea and vomiting, had become so severe for the first two days of each period that she remained home from work.

A physical examination revealed no abnormality. In the discussions it was noted that she was very lonely and found living in Washington different from life in a small town. She was also unsuited for her job. She was advised to make friends and to get other employment. After doing this her severe cramps disappeared.

2. This patient, 33 years of age, complained of progressive dysmenorrhea of eight months' duration. Prior to this she had never had menstrual difficulties. Physical examination revealed nothing abnormal. During the course of our discussion she disclosed that though she was married and had two children, for ten months she had been having sexual intercourse with another man. No contraceptives were used and each month, as the guilt and fear of pregnancy accumulated, the cramps became more painful. After she discontinued this illicit romance, her dysmenorrhea ceased.

Leucorrhea

Grafenberg¹¹ says that the psychogenic component of leucorrhea is little disputed. Bunnemann¹² reviewed a number of cases of leucorrhea reported in the literature as cured by suggestive therapy. Mayer¹³ particularly stressed the

psychogenic origin of leucorrhea and reported ten cases. By way of explanation he points out that unconscious sexual ideas are as likely to lead to hyperemia and hypersecretion in the genital region as are conscious ideas, the physiological effect of which is well known. Attention is often called to the psychogenesis of this symptom by the fact that it increases with excitation and decreases with distraction. The close association between the nervous endocrine system and the later effect on the genital tract readily explain the mechanism of leucorrhea.

Case Reports.—

1. A 30-year-old woman complained of leucorrhea. She previously had consulted two gynecologists who could find no reason for her symptoms. After a complete physical and bacteriological examination no cause for the leucorrhea was found. This patient was frigid and it was ascertained with difficulty that the discharge occurred when intercourse was anticipated. The discharge did not occur because of sexual excitement but because of an aversion to coitus. She would constantly tell her husband that she could not have intercourse because of the discharge. She was referred to a psychiatrist and after psychotherapy, the leucorrhea disappeared.

2. A 28-year-old woman had leucorrhea of approximately one year's duration. Examination on two different occasions failed to show any discharge. She returned about two months later still complaining of vaginal discharge. After further discussion, it was noted that it occurred only on days when her work brought her in contact with a certain man. Her relations with him had been only professional but further discussions revealed that she desired sexual relations with him. She was advised to change her job, which she did; her discharge appeared and had not returned when she was last seen, eight months later.

Vaginismus

The recognition of dyspareunia resulting from psychogenic causes is nothing new. Huguier,¹⁴ in 1834, wrote his thesis on vaginismus. Dupuytren,¹⁵ in 1839, recognized dyspareunia. Faure,¹⁶ in 1928, deplored the fact that prophylactic measures are rarely feasible and emphasized the effect of lack of love or of actual distaste in "arranged marriages" which are the rule in France.

It is obvious that fear of intercourse and aversion to it, are, generally speaking, the cause of this disturbance. The psychic etiology is manifold and often rather superficial. In psychogenic dyspareunia of long duration, great caution must be exercised in attempts at treatment. The attitude of the patient is decisive; only those who manifestly wish to be cured should be treated. Those in whom the defense and resistance conflicts predominate, should be referred to a competent psychiatrist.

Case Reports.—

1. A patient, 24 years of age and married two years, came in to be fitted with a diaphragm. No complaints were elicited during routine history which included direct questioning as to sexual relations. When pelvic examination was attempted an intact hymen was encountered. When further questioned, she revealed that the real reason she came was because of her inability to have sexual intercourse. The hymen was incised under Pentothal anesthesia with dilation of the vaginal introitus. She returned two weeks later to be fitted with a diaphragm, which was very difficult to accomplish because of spasm of the levator muscles. When she was questioned further, it was learned that at the age of seventeen she had attempted intercourse, after which she thought she was pregnant, and so told her mother. The guilt associated with this incident had made it impossible for her to relax during intercourse. After discussion and practice in introducing the diaphragm, intercourse became possible and eventually she had orgasms.

2. A patient, aged 25 years, complained of painful intercourse which had become progressively worse since her marriage nine months before.

Pelvic examination failed to reveal any cause for her pain. After some questioning it was learned that she had been in love with another man prior to her marriage but that her mother and sister had insisted that she marry her present husband because of his family connections. Though her husband was very kind and considerate and she respected him, there was no physical attraction.

The patient was not seen again until two years later, when she reported because of pregnancy. She had divorced her husband and married the man she loved. She had no further painful intercourse and was very happily married.

Summary and Conclusions

Recent psychologic experience has definitely proved that gynecologic disorders are often due to emotional disturbances. In the absence of organic pathology, the gynecologist must carefully review the patient's history in order properly to evaluate emotional factors related to her particular problem.

In the series of cases reported, psychotherapy on the conscious level frequently suffices for the cathartic effect to give the patient relief. If the conflict is deeply rooted, it is out of the realm of the gynecologist and should be referred to the psychiatrist.

Even if endocrine disturbances are noted, they may be secondary to the emotional factors.

A great part of gynecologic practice is concerned with proper evaluation of emotional and organic disturbances. The gynecologist must have good insight into the psychic factors which alter the function of the female genital organs in order to provide his patient with the best of care.

References

1. Walthard, Max: Psychotherapie. In: *Biologie und Pathologie des Weibes*, hrsg. Von Halban U. Seitz. Berlin und Wien, 1924, Urban und Schwarzenberg, Bd. ii, pp. 697-746.
2. Graefe, M.: *Zentralbl. f. Gynäk.* 43: 201-204, 1919.
3. Walthard, Max: See Ref. No. 1.
4. Allbutt, T. C.: *Lancet* 1: 459-509, 1884.
5. Menninger, K.: *J. Nerv. & Ment. Dis.* 89: 514, 1939.
6. Chadwick, Mary: *Nerv. and Ment. Dis. Monograph Series No. 56*, 1932.
7. Menninger, K.: See Ref. No. 4.
8. Novak, J., and Harnik, M.: *Zentralbl. f. Gynäk.* 53: 2976-2987, 1929.
9. Wittkower, E., and Wilson, A. T. M.: *Brit. M. J.* 2: 586, 1940.
10. Lewis, Thomas: *Pain*, New York, 1942, The Macmillan Company.
11. Grafenberg, E.: *Allg. Arztl. Ztschr. f. Psychotherap.* 2: 665-680, 1929.
12. Bunnemann, O.: *Therap. d. Gegenw.* 62: 132-136, 1921.
13. Mayer, A.: *Psychogene Störungen der Weiblichen Sexualfunktion*. In: O. Schwarz: *Psychogenese und Psychotherapie Körperlicher Symptome*, Wien, 1925, Springer, pp. 295-344.
14. Huguier: Cited by Faure and Siredey.¹⁶
15. Dupuytren: Cited by Faure and Siredey.¹⁶
16. Faure, J. L., and Siredey, A.: *Traite de Gynecologie*, ed. 4, Paris, 1928, Octave Doin, p. 565.

1150 CONNECTICUT AVENUE, N.W.

PSYCHOSOMATIC FACTORS IN FUNCTIONAL AMENORRHEA

W. S. KROGER, M.D., AND S. C. FREED, M.D., CHICAGO, ILL.

THE psychosomatic approach to the diagnosis and treatment of functional amenorrhea consists of a combination of psychologic and physiologic concepts. It is these aspects that seem to be neglected in the gynecologic literature. Too little attention is paid to the psychogenesis of this type of amenorrhea because of the physician's inadequate training for this phase of clinical medicine. There is no longer doubt that emotions may affect the endocrine system. It has been demonstrated that certain psychic states such as rage and fear in animals and in human beings increase the secretions of several ductless glands.^{1, 2, 3} Mental disorders, fears or anxieties, depression, and psychic trauma of various sorts may disturb the normal pituitary dominance over the thyroid, adrenal cortex, and ovaries. Hyperthyroidism, essential hypertension, and menstrual disorders may result from a disturbance of these, respectively. In regard to the ovaries, every physician has encountered patients in whom an emotional upset has produced amenorrhea for days, months, or years. In some, the menses are resumed when external disturbing factors are eliminated. In others, the cause is deeply rooted in the subconscious. Physicians fail to realize that subconscious factors may be just as effective in the production of amenorrhea as recognizable nervous manifestations.

Physiology of the Neuro-endocrine System

That the nervous system can influence the gonadotropic function of the anterior hypophysis is indicated by the following experimental and clinical evidence.

Psychic traumas also may produce derangement of the normal hormone patterns resulting in the suppression of hypothalamic influences on the anterior pituitary gland. Overt or latent psychologic disturbances may prevent release of luteinizing hormones. In the absence of the luteinizing factor, the ovarian follicle, although affected by the follicle stimulating hormone (F.S.H.) does not produce ovulation.⁴

Fremont-Smith⁵ suggests that amenorrheic women completely lack luteinizing hormone. Absence of the hypothalamic stimulus, which normally brings about the pituitary release of the luteinizing hormone, is suggested as the probable reason for this type of amenorrhea. Such hypothalamic inhibition is believed to result from emotional factors. Estrogen production and normal cyclic periods usually return following relief of emotional tension.

Questions still unanswered include the possible primary role of the endometrium, which is immediately responsible for menstruation. Markee⁶ has shown that in the monkey fright can arrest bleeding in ocular endometrial transplants, and that they respond to definite emotional influences. Loeser⁷ reported four cases of amenorrhea due to emotional shock. In all, histologic examination of biopsy specimens showed endometrium in the stage of de-

velopment it would have normally reached at the time of shock, suggesting that shock caused an immediate arrest of development by interruption of the release of the proper hormones.

The uterus contains an abundance of nerves throughout the myometrium which make connections with branches of the uterine artery, especially in the inner fourth of the myometrium where they join with a series of radial arteries, providing a nervous tissue medium for affecting control of the vascular phenomena associated with uterine physiology.⁸ Evidence that substantiates these hypotheses is advanced by Sher⁹ who believes that the hypothalamus probably governs our emotional responses to external environment, that response being expressed through the hypothalamic, sympathetic, and parasympathetic nervous systems.^{10, 11} Hypothalamic stimulation produces automatic discharge, the final effect being dependent on the preponderance of sympathetic or parasympathetic fibers.¹²

A more direct neurogenic control of uterine bleeding may also exist. Soskin and co-workers¹³ have shown that, in certain delayed cycles in otherwise normally menstruating women, bleeding may be induced by the injection of Prostigmine. During pregnancy, injection of the drug is not followed by bleeding, nor does such bleeding follow the use of Prostigmine in amenorrhea due to gross endocrine disturbance. His observation suggests, since the autonomic nervous system is closely associated with the emotional centers, that integration between psychic activity and uterine physiology may be mediated not only through hormonal changes, but also by direct neurogenic control of endometrial vascularity.

Nervous pathways to ovarian function are also illustrated in cats and rabbits which do not ovulate after copulation if the hypothalamic-pituitary nervous pathway is cut. Rats and mice do not produce functioning corpora lutea except after copulation or instrumentation of the cervix.^{14, 15} Brooks¹⁶ suggests that coitus in the rabbit causes an impulse to travel down the hypothalamic-pituitary nervous pathway which releases luteinizing hormones.

Additional evidence of higher brain centers controlling pituitary and ovarian function in animals is the well-known influence of light on the production of hens' eggs, which is mediated through the autonomic nervous system.¹⁷ Ovulation can occur even when the ovaries are removed from their normal location and implanted elsewhere in the body.¹⁸ Here the hypothalamus is a vital link in the chain of stimulation, passing on to the anterior pituitary the impulse which leads to discharge of gonadotropins. Injury to certain areas in the hypothalamus can produce amenorrhea in the monkey and evokes degenerative changes in the hypophysis.¹⁶ The hypothalamus, perhaps by direct nervous connection, seems to have an important influence on pituitary function in all mammalian species.

So far as its regulation of the hypophysis is concerned, there is some evidence for either a direct nervous connection or a neuro-humoral mechanism between the hypothalamus and the anterior lobe of the hypophysis. Hypothalamic control of anterior hypophysial secretory activity is probably mediated, at least in part, by way of the autonomic nerves which accompany vessels to the gland.¹⁹ Therefore, psychic stimuli can activate the sex centers of the hypothalamus and thus affect the anterior lobe secretions. Hence, the hypothalamus is the neuroglandular instrument and integrating center in command of the periodicity of menstrual rhythm. Fuerstner,²⁰ discussing the neurophysiology of the menstrual cycle and the role of the hypothalamus, believes that emotional factors may interfere with the rhythmic impulses of the hypothalamus, enabling the autonomic nervous system to produce a direct effect upon the uterine endometrium, thus bypassing the normal stimulation via

the endocrines. The idea that the pituitary gland is the "generalissimo of the endocrines" is not now entirely true, and it may be subservient to the hypothalamus.

It can no longer be denied that psyche and soma form an inseparable unit and that any disturbance in one sphere will have an effect on the other. Each patient presents both components. If one is exaggerated in some patients and diminished in others, both are invariably present if sought for and recognized.

Psychodynamic Factors

A brief review of the psychosexual factors responsible for menstrual dysfunctions will allow a better understanding of the psychodynamics of this condition. Every little girl passes through the phallic period, when she wishes she had been a boy. She develops intense feelings centered around the lack of a penis, thus inducing jealousy of all males. Although jealousy of the male may be wholly or partially repressed in women who remain fixated at the phallic period of their childhood, it manifests itself in general hostility toward males and a denial of their own sex. Unconsciously they feel that the vagina is a gaping wound and that they have suffered injury or mutilation as punishment for earlier childhood sexual conflicts.

Menstruation in addition to reactivating these early conflicts confirms the lack of a penis, thus establishing—in spite of their efforts to deny it—their femininity. Gill²¹ states that these women regard menstruation as a badge of femininity, and in their unconscious mind it is symbolic of an inferiority and deficiency. In our culture they feel "that this is a man's world" and intensely resent the "limitations" imposed upon them by menstruation and all it implies. After the phallic period the little girl's first genuine sexual striving is directed toward her father (Oedipus conflict). This desire now being unacceptable must be repressed (incest taboo). Unsuccessful resolution of this Oedipus conflict may result in pathological aftereffects.

To these women, menstruation unconsciously produces anxiety and hostility due to the frustration of their desire to have a penis. Since the ego is unable to handle these emotions on a conscious level, the tensions generated by the conflict may be expressed in a physiological dysfunction. In such disturbances the tension produced by unconscious anxiety selects a visceral outlet (organ neurosis), and may utilize organic discharge possibilities which result in symptoms.

One must understand women's mental defense mechanisms to realize why the uterus is unconsciously chosen. Simmel²² states that the unconscious selection of organs for the placement of repressed instinctual drives is not fortuitous. It is basically determined by repressed unconscious wish phantasies and often associated with infantile irrational concepts of bodily functions. When such drives are psychologically repressed and can be neither expressed in words and behavior nor recognized and counteracted, they exert an influence on the physical and psychological processes of the body and effect tissue changes in the female genital tract.

Hence, it is readily recognized that emotional stimuli of auto- or hetero-suggestive origin, if repressed, can produce alterations in the neuro-endocrine system, resulting in a somatic menstrual dysfunction, i.e., functional amenorrhea.

Diagnosis

The diagnosis of functional amenorrhea is usually made in the absence of organic, endocrine, or nutritional factors. If a psychological disturbance preceded the cessation of the menses, the diagnosis is facilitated. Some

etiologiical factors to be considered are: death of a loved one, shock or accident, emotional tension provoked by argument, change of climate and occupation, sexual maladjustments, and the wish to get pregnant (pseudocyesis). Fear of an unwanted pregnancy may also produce amenorrhea. Gill²¹ states that behind the conscious fear of pregnancy may be the deeply repressed wish to bear a child. Onset of the menses allays the woman's fears, substantiates the existence but also the influence of psychological factors.

The diagnosis is difficult in those who have latent psychological disturbances, since these are on an unconscious level. Competent psychiatric consultation may be necessary for this type of case, even though a thorough investigation of the emotional factors involved in psychogynecic complaints is difficult when there is too much division of authority. The gynecologist should be his own psychiatrist in the majority of cases. He can arrive at the correct psychodynamic diagnosis of his patient's symptomatology if he invests himself with the necessary psychological knowledge. Menninger²³ aptly said, "The effects of the human body make it imperative that every individual practicing medicine be as well grounded in the anatomy, physiology and pathology of the psyche as he is in that of the soma."

Treatment

A complete and tactfully elicited history of each case is most important. Evaluation of all of the patient's complaints is imperative. The gynecologist must study the woman suffering from amenorrhea psychologically as well as organically. Psychotherapy must be based on the sound principles of internal medicine and psychodynamics. The psychodynamic approach concerns the patient as an individual, focusing the treatment on her rather than on external factors. Basic causations must be elicited. Conscious or intellectual material is disregarded, and only unconscious material obtained through psychoanalytical techniques is considered in patients who have latent disturbances.

Frank discussion and sympathetic assurance, when the disturbance is relatively benign, can remove much of the pathogenic influence. Changing the faulty attitudes and erroneous beliefs of the woman can remove much of the mystery and apprehension surrounding menstruation. Because of the underlying emotional disturbances, hormonal therapy is usually disappointing, though psychologically helpful.

This type of "minor psychotherapy" is utilized by physicians committed to the organic approach, and who are unwilling and unable to see the psychodynamics responsible for functional conditions. They cannot comprehend the manifestations of the unconscious, the psychic mechanisms and processes, and the roles that symbolization plays in our lives. This organic approach may be justifiable for the patient, but the therapist should not delude himself as to the mechanism of cure.

In patients having a deeply rooted psychological disturbance, various other psychotherapeutic procedures may be utilized, i.e., hypnoanalysis or psychoanalysis. These measures are essential in such cases because they appeal to the emotional and physical makeup of the patient. These methods recognize the unconscious as the most dynamic aspect of life and directly attack the etiologiical factors responsible, and subsequently result in their dissolution.

Brief Psychotherapy

Let the patient tell her story, thus ventilating her pent-up emotions. The underlying forces producing the symptoms will be recognized. She must understand the mechanisms responsible for her unconscious conflict. Fortunately, this disturbance is not often caused by too deeply repressed uncon-

scious conflicts. It is usually precipitated by thought material that is only preconscious. Thought material is termed preconscious when it is suppressed and shifted only temporarily from the conscious perception of the ego which is unable to understand or interpret a specific conflict situation. Treatment is directed toward the patient's gaining insight into the emotional conflict (making conscious, unconscious material) and shifting the conflict from the soma (body) to the psyche (mind) where it belongs. Certain experiences are discussed with some patients releasing a psychic inhibition, thus liberating the normal hormonal processes. This type of patient uses a somatically expressed symptom as a psychological masquerade for her latent guilt feelings, anxiety, and other mental defense mechanisms which have been mentioned. She is sailing a psychological sea under a gynecological flag!

Dunbar,²⁴ quoting Mayer and Allers respectively, suggests that amenorrhea occurs as an expression of the "masculinity complex," i.e., the desire to be a man or not to menstruate. The latter, using a superficial type of psychotherapy, in five cases found a refusal to assume the feminine role which was deep seated and more or less consciously experienced. In these cases the menstrual disturbances disappeared after a change had taken place in the patients' personalities without therapeutic efforts directed specifically toward these disturbances. Every psychotherapist is aware of the amenorrheic woman who either betrays in her makeup the desire to be masculine or admits that she always wanted to be a "tomboy." Many cases show this psychic mechanism of amenorrhea.

Case Treated by Brief Psychotherapy.—

CASE 1.—Miss E. S., aged 18 years, had a history of amenorrhea since puberty. Physical examination was essentially negative. Hormonal therapy failed to bring on the menses. Careful questioning revealed the following facts: She hated her father, who periodically beat her mother; he drank excessively and bragged about his extramarital affairs. At an early age she identified herself with her mother. Though the family was wealthy, her two older sisters left because of the intolerable home situation. One married and the other "went out on her own." She confided that some day she would like to "get even" for the suffering that her mother got from her father. Under sympathetic instruction she was told that this was an abnormal relationship and that her father did not typify all men. The mother was advised to obtain a divorce but refused because she wanted security for herself and her remaining daughter. The daughter was advised to enter college away from home. Her attitude toward men and toward her father was readily corrected. Much of her nervous tension was relieved by the change in the environment. Normal menstrual periods ensued. At first the menses were irregular and scanty, but after one year they were normal and well established.

Hypnotherapy

The importance of hypnotic suggestion in treating psychogenic amenorrhea has been demonstrated by many investigators. Dunbar²⁴ states, "In many cases amenorrhea can be cured by one hypnotic session. In a patient who had been suffering from amenorrhea for two and one-half years, menses were induced by hypnosis, and regulated to occur on the first day of each month at 7:00 A.M. to last for three days."

Heyer²⁵ says: "Numerous authors report results from hypnotherapy in menstrual disturbances, which are beyond question, i.e., relief of pain as well as regulation of the cycle. As a matter of fact, the time of onset for menstruation can be determined in deep hypnosis to the day and hour, as for example, one may say every four weeks or every first day of the month, etc. . . . In all uses of hypnosis it is important to give not just colorless commands, but to suggest the whole experience of menstruation forcefully and vividly. Where

doubt as to the efficiency of this procedure has arisen, faulty technique is responsible." We, too, have frequently postponed or induced the menses by hypnosis.

However, hypnosis is only symptomatic therapy, and if the basic emotional difficulties are not eradicated, other symptom-equivalents, i.e., dysmenorrhea, migraine or backache, and pelvic pain will be somatically utilized. The skill utilized in handling the relationship between the therapist and patient, and the interpretation of the ventilated material is of paramount significance. The following case is presented to demonstrate the intimate relationship between the psyche and menstruation. In selected cases this procedure is therapeutic.

Case Treated by Hypnosis.—

CASE 2.—Miss. M. H., aged 24 years, presented a history of amenorrhea of six years' duration. The symptom began when she entered nurse's training. She failed to menstruate after receiving a wide variety of hormonal therapy. Physical examination was essentially negative. Menses began at 13 years, regular; no pain; four to five days' duration. Hypnosis was induced. The subjective and objective symptoms of menstruation were described. She was given posthypnotic suggestions that she would menstruate in two weeks and that she would remember in minute detail the description of the posthypnotic suggestions concerning the prodromata of the menses as well as the signs and symptoms of the actual onset. To the patient's surprise, she reported that the menses were resumed exactly two weeks after the induction of hypnosis. Menses continued normally for ten months. The patient returned stating she had missed one period. Questioning revealed that she had intercourse with her fiancé several weeks before her anticipated menstrual period. An Aschheim-Zondek test was negative. Hypnosis was induced and the same procedure repeated. Again the menses were resumed, but a week earlier than suggested. Menses remained regular and the patient was discharged. The patient was seen six years later. She had married and was menstruating regularly.

Simple suggestions and assurance might have produced the same result, but the effects of scientifically induced suggestion embodied in hypnosis is unquestionably more efficacious. No attempt to use more than suggestive therapy was utilized in this case.

Hypnoanalysis

Hypnoanalysis elicits underlying psychogenic and behavior disorders and enables the therapist and patient to ascertain the factors responsible for the symptom-complex. It penetrates below the resistances of the patient and is helpful in integrating, synthesizing, and enforcing new and more wholesome attitudes. Also, new personality patterns can be engrafted. Most important of all, it speeds up an ordinarily slow process.

Lindner²⁶ states that hypnoanalysis can be described as an incisive approach which, more rapidly than other psychotherapeutic methods, cuts to the core of psychogenic and behavior disorders and enables the therapist to come to grips with the root causes in the dynamics of the disorder confronting him. Hypnoanalysis, indeed, is mental surgery.

We have already demonstrated that hypnoanalysis is a relatively short and effective treatment when properly applied in functional gynecologic disorders,^{27, 28, 29} and described the various techniques.³⁰

Under hypnoanalysis the patient's thoughts (free association) are spontaneous and unfold with ease. This freedom of behavior illustrates one of the most important aspects of hypnoanalysis. A wide latitude of expression is produced. The patient is not subservient, unconscious, or helpless. The ego of the patient with its resistances and defenses is involved when hypnoanalysis is utilized; therefore, the insight gained is assimilated and a significant change takes place in the ego. During age regression, the patient's actions

show the vividness with which she relives traumatic experiences. This "abreactive method" is a reliving of original experiences which takes place in the present framework of her consciousness. The patient's recognition and reliving of old behavior patterns is one of the ways she obtains "insight." She must understand the origin and basis of her symptoms, how they are linked up with life's experiences, childhood pattern formations, and unnatural inhibitions. The symptom-complex of functional amenorrhea will disappear only when its symptomatic meaning has become clear to the patient.

The hypnoanalytical technique is more rapid than most other methods of psychotherapy because the resistances of the patient are by-passed. It operates directly upon the conflict, and if this is solved, many of the defenses will spontaneously disappear. The following case history demonstrates the effectiveness of this procedure in a severely disturbed patient.

Case Treated by Hypoanalysis.—

CASE 3.—Mrs. H. L., aged 34 years, married eleven years, was seen with history of nervousness, fatigue, and amenorrhea of six months' duration. She had two children, eight and three years of age.

Patient had a "nervous collapse" three weeks prior to admission. Her physician gave her "shots" and sedatives and told her "not to worry." During the first interview she stated that she had horrible nightmares and a desire to "cut up my little 3-year-old son." She feared being alone with the child. Because this patient obviously had a deep-seated nervous disorder, hypoanalysis was advised. After several sessions she became a good hypnotic subject. During subsequent hypnotic sessions, she admitted her lack of sexual enjoyment. She was frigid most of the time and especially since the birth of her son. The past history revealed that her mother died when she was six years old, leaving seven children. The father remarried and her stepmother had two more children. She felt very close to her father and identified herself with him until he remarried. As a result, she developed marked hostility toward him. She hated and resented her stepmother and keenly felt the loss of her own mother. At twelve, she asked about her brother's circumcision and her stepmother reprimanded her saying, "How do you know about such things?" She was kept ignorant of all sexual matters for many years; for this she blamed her stepmother, and indirectly, her father. She often thought that all men were bad.

The psychosexual history obtained under hypoanalysis revealed her infantile and adult masturbation and her natural sexual inquisitiveness. The material obtained in the following hypnotic sessions demonstrated further unhealthy attitudes. At seven, a clerk in her father's store used to "cop a feel" of her genitals. At twelve, her brother had intercourse with her. This experience made her hate him. Menses began at 13 years; they made her "sick" because they interfered with her athletic activities; she could no longer play baseball and swim with the boys. She was a "tomboy" until the age of 18 years, when she began to date young men. At twenty, a boy raped her and she became hysterical after this experience. She became extremely shy following this traumatic episode, felt very guilty, and avoided people. She felt people were watching her. She then left town to earn her own livelihood. In a new environment she felt better, but "all men were beasts." After several years she met her present husband, and after dating him for a year, she married him. She had several "affairs" with him prior to her marriage, one of which necessitated a criminal abortion. She was frigid at all times, both prior to marriage and for four years afterward. At this time the man who raped her was killed and following news of this, sex became enjoyable. One year later she gave birth to her daughter. She identified herself with her daughter and even hoped for a girl during her second pregnancy. This pregnancy was accompanied by considerable anxiety, nausea and vomiting. The advent of a son into the family constellation represented a threat to an already precarious existence with her husband. The arrival of the boy infant was a tremendous disappointment, and she became enraged when her mother-in-law

sent her a bouquet commenting, "Now we are finally grandparents in name." The husband was extremely partial to the infant, making her daughter so insecure that she had nocturnal enuresis.

Subsequently hypnoanalytical sessions gave the patient insight into her ambivalent feelings toward her husband; the emotional factors producing her frigidity which were based on her unconscious refusal to give herself sexual gratification and the nature of her compulsive feelings toward her son. She integrated the repressed material into her conscious ego; she realized that her resentment for the child was due to the hostility she felt toward all men. Her unsolved Oedipus conflict also produced additional persistent feelings of resentment toward men, which were then projected to her own son. She became aware of her faulty attitudes toward menstruation, which in reality were an unconscious repudiation of her femininity. She also recognized her guilt feelings over her infantile masturbation, and her early sexual curiosity and experiences.

After thirty-five sessions during which the various techniques of hypnoanalysis described in previous publications were utilized to give her further insight, the patient began to have vaginal orgasms. She felt closer to her husband and children than ever before and soon resumed her normal menstrual periods which have been normal until the present time.

Discussion

The above theories indicate that functional amenorrhea often may be on a psychogenic basis. Examination of the patient requires additionally a study of the habit patterns and attitudes of the patient. The ignorance of psychotherapeutic methods does not justify the indifference of the gynecologist toward ascertaining the psychogenic factors producing or accentuating the symptom-complex of amenorrhea. Insight into the emotional conflicts of the patient is the *sine qua non* of therapy.

The gynecologist must take the psychogenic factors into consideration in order to understand the etiology of this symptom-complex, and to determine the type of therapy he will employ. The gynecologist can be taught the simpler techniques, i.e., brief psychotherapy which can be used in early cases. He must know when to implement his gynecological therapy with adequate psychotherapy. If unable to perform the latter, he should refer the case to a competent psychotherapist or to a gynecologist so oriented.

An understanding of neurophysiological mechanisms provides a more reasonable explanation for this type of menstrual disturbance. Also, in many cases, it would account for the response to treatment by the numerous endocrine preparations. These may be effective in a great many cases of amenorrhea on the basis of unintentional suggestion.

Where the conflict is relatively deep seated, hypnoanalysis is a comparatively rapid and rational form of therapy in handling damaging emotions, thus providing discharges by way of motor pathways instead of internalization via the autonomic nervous system. Hypnoanalysis varies only in degree from psychoanalysis, since it utilizes many of the concepts of Freudian theory, i.e., interpretation of the transference, free association, piece-meal disintegration of the patient's resistances, reintegration into consciousness (assimilation by the ego) of the repressed material, and the redistribution of the psychological energies formerly exploited by the symptom-complex of functional amenorrhea; thus the patient gains insight into factors responsible for the symptom-complex.

The physician must not fail to recognize the influence of "operator attitude" on the patient, and the rapport and dependency situation inherent in every doctor-patient relationship, which is unconsciously sought for by the patient, especially in functional gynecological conditions.

It is not too difficult for gynecologists to avail themselves of sufficient psychiatric training to treat adequately cases of psychogenic amenorrhea. With careful diagnosis and the selection of suitable psychotherapeutic procedures, i.e., brief psychotherapy, hypnotherapy, and psychoanalysis, the treatment of functional amenorrhea will be gratifying to the physician and patient. These methods of treatment are the most rational and scientific, since it is only with these that the specific etiological factors of this disorder can be properly evaluated and corrected.

We wish to express our appreciation to Dr. B. P. Morales for his interest and helpful suggestions.

References

1. Cannon, W. B.: *Bodily Changes in Pain, Hunger, Fear and Rage*, ed. 2, New York, 1936, D. Appleton-Century Company, Inc.
2. Cannon, W. B.: *Ann. Int. Med.* **9**: 1453-1465, 1936.
3. Reifenstein, E. C.: *M. Clin. North America* **30**: 1103, 1946.
4. Klinefelter, H. F., Jr., Albright, F., and Griswold, G. C.: *J. Clin. Endocrinol.* **3**: 529-544, 1944.
5. Fremont-Smith, M., and Meigs, J. V.: *AM. J. OBST. & GYNEC.* **55**: 1037, 1948.
6. Markee, J. E.: *Contrib. Embryol. (No. 177)* **27**: 233, 1944.
7. Loeser, A. S.: *Lancet* **1**: 518-519, 1943.
8. Hirsch, E. F., and Martin, M. E.: *Surg., Gynec. & Obst.* **76**: 697-702, 1945.
9. Sher, N.: *Brit. M. J.* **1**: 347, 1946.
10. Masserman, J. H.: *Am. J. Psychiat.* **98**: 633, 1941.
11. Tucker, B. R.: *South. M. J.* **34**: 124, 1941.
12. Gellhorn, E.: *Am. J. of Psychiat.* **97**: 944, 1941.
13. Soskin, S., Wachtel, H., and Hechter, O.: *J. A. M. A.* **114**: 2090, 1940.
14. Freedman, M. H.: *Am. J. Physiol.* **89**: 439, 1929.
15. Greulich, W. W.: *Anat. Rec.* **58**: 217, 1934.
16. Brooks, C. McC.: *The Hypothalamus and Central Levels of Autonomic Function*, Baltimore, 1940, The Williams and Wilkins Company.
17. Clark, L. B., Leonard, S. L., and Bump, G.: *Science* **85**: 339, 1937.
18. Smith, P. E., and White, W. E.: *J. A. M. A.* **97**: 1861, 1931.
19. Globus, J. H., Goldfarb, A. I., and Silver, S.: *J. Mt. Sinai Hosp.* **14**: 315, 1947.
20. Fuerstner, P. G.: *J. Nerv. & Ment. Dis.* **99**: 588-594, 1944.
21. Gill, M.: *Bull. Menninger Clin.* **7**: 12, 1943.
22. Simmel, El.: *California & West. Med.* **63**: 169-174, 1945.
23. Menninger, W. C.: *Diplomate* **19**: 69, 1947.
24. Dunbar, F.: *Emotions and Bodily Changes*, New York, 1938, Columbia University Press, p. 335.
25. Heyer, G. R.: *Hypnose und Hypnotherapie in Die Psychischer Heilmethoden* Hrsg. von Karl Birnbaum, Leipzig, 1927, Georg Thieme, pp. 73-135. Quoted by Dunbar.²⁴
26. Lindner, R. M.: *Dis. Nerv. Syst.* **6**: 371-374, 1945.
27. Kroger, W. S., and Freed, S. C.: *AM. J. OBST. & GYNEC.* **46**: 817-822, 1943.
28. Kroger, W. S., and DeLee, S. T.: *AM. J. OBST. & GYNEC.* **51**: 544-552, 1946.
29. Kroger, W. S., and DeLee, S. T.: *AM. J. OBST. & GYNEC.* **46**: 655-661, 1943.
30. Kroger, W. S.: *AM. J. OBST. & GYNEC.* **52**: 409-418, 1946.

104 SOUTH MICHIGAN AVENUE, CHICAGO, ILL.
450 SUTTER STREET, SAN FRANCISCO, CALIF.

THE SEPTIC ABORTION KIDNEY

J. P. WYATT, M.D., F.C.A.P.,* AND H. GOLDENBERG, M.D., TORONTO, ONTARIO

(From the Departments of Pathology and Gynaecology, Toronto East General Hospital)

SINCE Bywaters^{1, 2} and his associates drew attention to the distinctive renal lesions found in fatal cases of "crush syndrome," similar or identical changes have been observed in a variety of conditions. The lesions of this type of nephrosis have been noted following severe trauma to muscle, nontraumatic muscle ischemia, burns, heat stroke, excessive dehydration, intravascular hemolysis, intoxication due to sulfonamides and a variety of poisons and "shock" from many causes.

Balduin Lucké³ introduced the morphopathogenic term of lower nephron nephrosis, to describe the characteristic renal lesions found in these various conditions, which have in common destruction of tissues or blood, with or without shock, and the clinical sequel of acute renal insufficiency. The tissue alterations are principally degeneration in the distal segments of the nephron and collecting tubules and intraluminal heme casts. Other descriptive terms applied to this morphologic entity include: crush syndrome or anuria, hemoglobinuric nephrosis, pigment nephrosis, traumatic anuria or uremia, renal anoxia or tubulovascular syndrome of Maegraith.^{4, 5}

Lower nephron nephrosis has been rarely reported in fatal cases of septic abortion, possibly being overlooked because of the other more obvious and dramatic changes in the pelvic organs. The purpose of this communication is to point out the similarity between the septic abortion kidney and other diverse etiological entities which may lead to pigment nephropathy. Three cases of lower nephron nephrosis following septic abortion in young women are herein briefly reviewed. Certain outstanding features were common to all: induced septic abortion at 10 to 14 weeks of pregnancy, with shock and uteroplacental damage, and the sequel of renal shutdown with acute insufficiency, terminating fatally in eight to eleven days.

CASE 1.—P. K., a 25-year-old, single woman, whose last normal menstrual period was Nov. 1, 1946, developed crampy abdominal pains following an abortifacient douche of castile soap and castor oil on Feb. 6, 1947. This patient was admitted to hospital the following day with a blood pressure of 120/80, vaginal bleeding, and vomiting. The abdomen was rigid, especially in both lower quadrants, and associated with extreme tenderness. Penicillin therapy was immediately instituted. There was a previous history that following the illicit douche, the patient "went flat" in a taxi and was brought to the Admitting Department of the hospital. On February 9, a 2½ months' infected fetus was passed. Urinalysis was acid in reaction, with a specific gravity of 1.020, albumin 2 plus, negative for sugar, benzidine positive, and a few white blood cells.

The following day the patient recommenced vomiting, suffered a chill and a rigor with a temperature of 103° F. Throughout the remainder of her fatal course in hospital, she ran a septic temperature. Sulfathiazole therapy was instituted but was discontinued after twenty-four hours. The blood level reached 6.0 mg. per cent. By February 12, the vomiting was protracted, the lower limbs and labia majora were markedly edematous, and the

*Now at Department of Pathology, St. Louis University, St. Louis, Mo.

abdomen was still rigid. On February 15, the patient's condition rapidly deteriorated and passed from an oliguric phase to an anuric one. On this date, a transfusion of 500 c.c. of fresh compatible group "O" Rh-positive blood was given. The urinalysis remained acid in reaction with a fixed specific gravity. The blood nonprotein nitrogen steadily rose to reach 179 mg. per 100 c.c. on February 17. The icteric index was 6 units. The white blood count climbed from 11,400 on admission to a terminal leucocytosis of 38,500 per c.mm.

Despite penicillin, forced fluids, and alkalies, this patient died from uremia and generalized peritonitis.

The daily fluid intake and urinary output charted as follows:

DATE	INTAKE	OUTPUT
Feb. 7	1,470 c.c.	150 c.c.
Feb. 8	2,720 c.c.	60 c.c.
Feb. 9	2,540 c.c.	120 c.c.
Feb. 10	420 c.c.	180 c.c.
Feb. 11	2,510 c.c.	210 c.c.
Feb. 12	910 c.c.	165 c.c.
Feb. 13	5,040 c.c.	420 c.c.
Feb. 14	4,385 c.c.	210 c.c.
Feb. 15	3,950 c.c.	90 c.c.
Feb. 16	1,440 c.c.	60 c.c.
Feb. 17	670 c.c.	60 c.c.

Pathological Findings.—Septic abortion, acute abortal endometritis, acute salpingo-oophoritis, septic thrombophlebitis of parametrial and femoral veins, localized peritonitis with adhesions of bowel to uterus; 500 c.c. of serosanguineous peritoneal effusion, lower nephron nephrosis, edema of lungs, bilateral pleural effusions, cloudy swelling and central necrosis of liver, acute splenitis. No evidence of abortifacient paste pulmonary embolism.

From the standpoint of therapy, the question arises whether in this case, too much fluid may have been administered contributing to the intense edema of the lungs. At the time of the blood infusion, the patient already presented the well-advanced clinical moiety of lower nephron nephrosis so that the blood transfusion may possibly have been a detriment in the treatment of this case in view of the fact that existent free plasma hemoglobin even in fresh blood would fall upon an already damaged tubular mass.

CASE 2.—E. J., a 26-year-old woman with a past history of four self-induced abortions, was admitted to hospital on March 23, 1948, with a history of having fallen downstairs, followed by crampy lower abdominal pain and vaginal bleeding for two days. One month prior to admission, it was known she had attempted to procure an abortion by the use of a Lysol douche.

On admission, the abdomen was rigid and tender. The patient's temperature was normal, the hemoglobin 65 per cent, and the urine alkaline with a trace of albumin. Bleeding was slight and she was treated as having a threatened abortion. However, three days after admission, she passed a macerated fetus measuring 9 cm. from crown to rump. The following day under Pentothal, cyclopropane, and oxygen, the uterus was gently curetted but little tissue obtained.

During her course in hospital, the urinary output remained low. Her fluid intake, however, was inadequate. She became listless, drowsy, and uncooperative, and could not be kept awake for more than two minutes at a time. The urinary suppression persisted and by March 30, the nonprotein nitrogen was 243 mg. per cent. Urinalysis revealed albumin 4 plus, "crenated red blood cells" 18 to 20, and white blood cells 4 to 5 per high-power field. Terminally an intravenous solution of 10 per cent glucose in distilled water was given but to no avail. She could not retain fluids by mouth and was troubled with nausea and vomiting. Her condition rapidly deteriorated and she died on March 31, eight days after admission. During her course in hospital, she ran a septic temperature fluctuating between normal and 102° F. On the day of death, the patient's white blood count was 9,900, hemoglobin 50 per cent, the temperature normal, but the pulse rate 105.

The fluid intake and urinary output were charted as follows:

DATE	INTAKE	OUTPUT
March 23	120 c.c.	0 c.c.
March 26	660 c.c.	60 c.c.
March 27	360 c.c.	0 c.c.
March 28	330 c.c.	120 c.c.
March 29	300 c.c.	30 c.c.
March 30	2,380 c.c.	150 c.c.

Pathological Findings.—Septic abortion (4½ months), acute parametritis, right salpingo-oophoritis, acute generalized peritonitis, paralytic ileus, septic thrombophlebitis of parametrial, right internal iliac, ovarian, and uterine veins, recent pulmonary emboli in all branches of right lower lobe, lower nephron nephrosis, acute splenitis, cloudy swelling of liver and central necrosis, edema of lungs, bilateral pleural effusion, focal vaginitis, bilateral renal papillitis. No evidence of embolic abortifacient paste products in lung capillaries.

In this case, it is our contention that far too little fluid was administered. The complication of dehydration no doubt aided and abetted the setting up of the syndrome of lower nephron nephrosis.

CASE 3.—L. W., a 32-year-old woman, was admitted to hospital on Oct. 29, 1947, complaining of lower abdominal pain and vaginal bleeding for two days following interference with pregnancy by a lay abortionist. Amenorrhea had been present for two months. Prior to admission, a few tablets of a sulfonamide had been taken.



Fig. 1.—Kidney. Weight 210 grams. Swollen pale cortex with clear demarcation from dark prominent medulla. (Two-thirds life size.)

Examination revealed abdominal distention and generalized tenderness. Pelvic examination was painful. Laboratory investigation on admission showed a blood nonprotein nitrogen of 233 mg. per cent, a carbon dioxide combining power of 14 per cent, a blood sulfonamide

level of 5.3 mg. per cent, and an acid urine benzidine positive with albumin 1 plus and 8 to 10 white blood cells per high-power field. The patient's urinary output for the first two days in hospital was 2,300 c.c. Following this, the output varied between 60 c.c. and 240 c.c. daily.

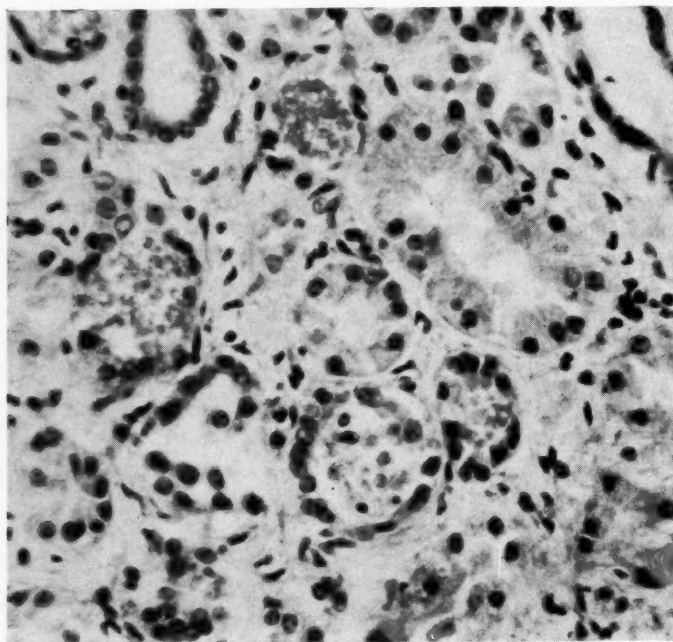


Fig. 2.—Kidney. Necrosis of cells lining tubules and fine granular pigment within lumina. ($\times 210$.)

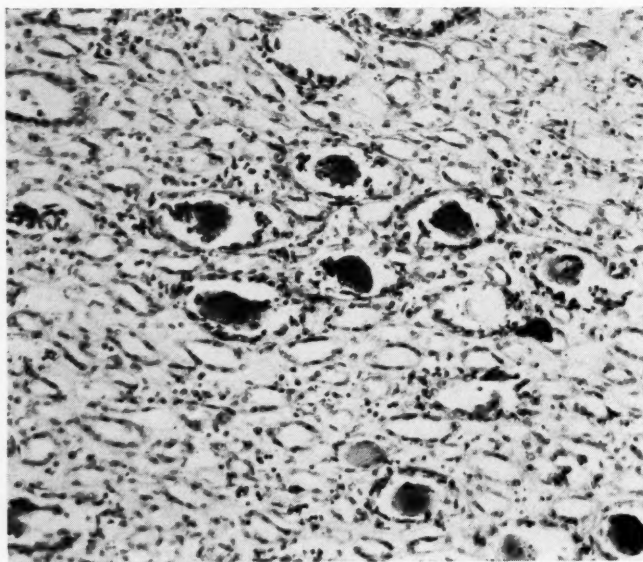


Fig. 3.—Kidney. Prominent amorphous dark casts plugging distal and collecting tubules. ($\times 120$.)

Despite intravenous therapy and forced fluids, the nonprotein nitrogen remained elevated between 225 and 250 mg. per cent. The patient developed convulsions on Nov. 4, 1947, and died.

Pathological Findings.—Septic abortion, acute abortal panmetritis, parametritis, thrombophlebitis of right ovarian and right common iliac veins, lower nephron nephrosis, bronchopneumonia of right lower lobe, infarct of lung in left lower lobe, pleural effusions, 500 c.c.

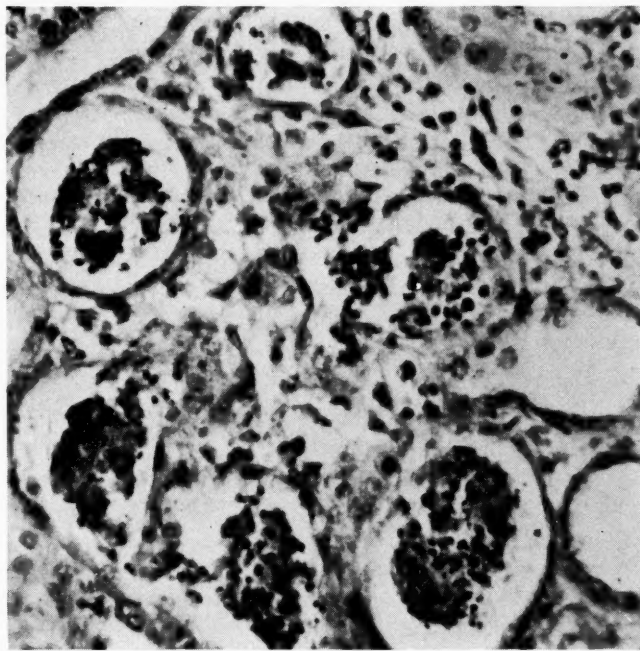


Fig. 4.—Kidney. Admixture of neutrophilic leucocytes and amorphous pigment forming casts blocking numerous tubules. ($\times 320$.)

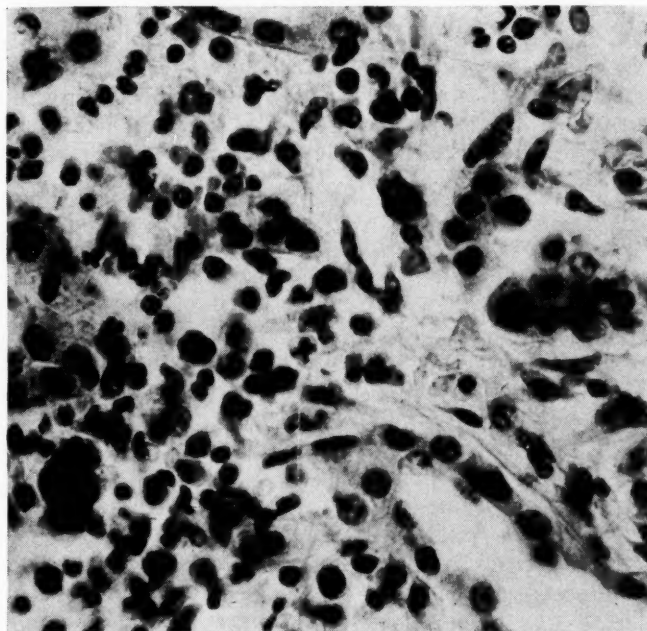


Fig. 5.—Kidney. Interstitial granulomatous reaction showing giant cells, plasma cells, and leucocytes. ($\times 400$.)

of fibrinous exudate in right chest cavity and 1,000 c.c. of bloody fluid in left. No foreign pulmonary intravascular embolic products were encountered.

This case history indicates the rapidity with which the kidney complication can develop in a neglected criminal abortion and on admission to hospital present a full-blown clinical lower nephron nephrosis due to the sudden interruption of pregnancy.

The kidneys from these three cases presented a characteristic appearance (Fig. 1). The kidneys were enlarged, each over 200 grams. The subcapsular surface was smooth and a pale mottled brownish-yellow, sometimes showing a few petechiae. On section, the cortex was pale yellow and swollen. There was clear demarcation between the cortex and the chocolate-red medulla. There were occasionally small hemorrhages in the pelvis. On histological examination, there was considerable degeneration of the tubular epithelium (Fig. 2), with necrosis of individual cells and occasionally of the lining of the whole tubule or even small groups of tubules. Apart from the protein precipitate in the capsular space, the glomeruli were unaffected. Casts were numerous throughout (Fig. 3), but especially in the collecting and discharging tubules. Casts were made up of conglutinated brick-red material or brownish amorphous coils of heme pigment. Neutrophilic leucocytes were frequently present in the tubules forming pure leucocytic plugs or mingled with other casts (Fig. 4). Epithelial cells also formed casts. Atherocytosis of heme pigment was noted in the tubular lining cells. The interstitial tissue was edematous and numerous foci of subacute inflammatory reaction were found in relation to the "blocked" tubules (Fig. 5). These foci were most numerous in the intermediate zone of the kidney parenchyma. The vessels of the medulla were engorged.

Discussion

Following upon the description of the "crush syndrome" by British pathologists during the 1940-1941 blitz, James Young⁶ described a similar symptom-complex in two types of obstetrical conditions, in which massive damage affecting the placenta and uterine muscle or other pelvic tissues may be followed by renal insufficiency and azotemia. These two conditions are retroplacental hemorrhage and the trauma of labor. It is now clearly established that this syndrome is similar to that described for crush anuria, and includes: initial tissue damage, shock, severe, moderate, or even absent, urinary suppression leading to anuria or oliguria with urine containing casts and leucocytes, a rising blood urea reaching its height on the fifth to ninth day, followed by death, or by greatly increased urinary output with recovery and complete restitution of the kidney architecture.

Young⁷ observed that renal failure does not follow shock from other forms of obstetrical hemorrhage (that is, postpartum hemorrhage, placenta previa with hemorrhage, premature separation with visible hemorrhage). However, when hemorrhage is accompanied by extravasation of blood into the uterine tissue with trauma to muscle, renal impairment can be expected. This thesis was substantiated by Paxson, Golub and Hunter⁸ in 1946, when they reported lower nephron nephrosis in three obstetrical and gynecological cases which had in common extravasation of blood into tissues associated with little or no shock in two of the cases. They concluded that shock in itself was not the important causative factor. These cases included retroperitoneal hemorrhage, ruptured uterus with hemorrhage, twisted ovarian cyst with extravasation of blood.

In 1941, Bratton⁹ described nine fatal cases with urinary suppression or azotemia associated with a renal lesion similar to that found in traumatic anuria. All except one of these cases were in association with abortion or parturition and, of these, six were described as "septic abortion." In none had blood transfusions been given. There was tubular degeneration with hematogenous casts in five cases reminiscent of the histopathology found in lower nephron nephrosis. Humphrey and Jones¹⁰ and Fernandez and Fromm¹¹ have commented recently

on postabortal anuria. Young and Walker¹² have also described a case of the uremic syndrome after abortion which on post-mortem examination presented the accepted picture of pigment nephrosis.

O'Sullivan and Spitzer¹³ in 1946 reviewed seven cases of acute renal failure complicating abortion, two of which were fatal and examined post mortem. Of these, one was a case of septic abortion with which urinary suppression and azotemia developed. The kidneys at autopsy showed an appearance similar to those found in crush injury. This case was complicated by sulfonamide chemotherapy, blood transfusion therapy, and the post-mortem finding of *Clostridium welchii* infection. However, there was little evidence to incriminate these three factors in the production of the renal lesion. The second fatal case was one of abortion at twenty-four weeks of pregnancy, followed by renal insufficiency and death, with the autopsy findings of symmetrical cortical necrosis of the kidneys. Of the nonfatal cases, three followed septic abortion, while one was considered a rare case of symmetrical cortical necrosis of the kidneys with recovery.

It has long been known that hemoglobinemia and hemoglobinuria not infrequently occur in eclampsia of pregnancy associated sometimes with renal failure and a kidney lesion exhibiting blood pigment casts and tubular degeneration. Schmorl,¹⁴ in 1893, described the presence of yellow pigment in the collecting tubules of the kidney in two out of seventeen cases on which his classical monograph on "Pathology of Eclampsia" was based. Brutt and Shumm¹⁵ in 1918 reported six cases of eclampsia with hemoglobinemia in which hematin casts were present in the urine. In a fatal case, with marked oliguria, hematin casts were abundant in the straight and Henle tubules. In general, German writers regarded the hemolytic process as one of the side effects of the eclamptic poison, an effect which it shares with other abortifacient poisons, such as arsenic and quinine.

The role played by sepsis in the pathogenesis of the septic abortion kidney is not simple to assess. Infection, per se, has not been known to produce the lesions of lower nephron nephrosis unless it were associated with destruction of tissue or hemolysis of blood, or accompanied by shock. Mallory¹⁶ mentions a case of hemoglobinuric nephrosis resulting from a severe streptococcal infection.

Postabortal *Clostridium welchii* (gas gangrene) toxemia and septicemia, which usually follow the introduction of the organism during interference with the pregnancy, may result in gross red blood cell destruction and jaundice with the liberation of hemoglobin into the plasma and urine and cast formation. Rendle-Short,¹⁷ who recently reviewed *Clostridium welchii* infection of the uterus, described the presence of blood pigment and casts in the urine, but attention was not focused on any renal investigation or morphology.

Two acute renal lesions are observed in abortion which may follow utero-placental damage, shock, toxemia, or infection, and lead to renal failure. These two recognized conditions are the "septic abortion kidney" or lower nephron nephrosis, and symmetrical cortical necrosis (cortical sequestration) of the kidney. Although pigment nephrosis has been only rarely reported in fatal cases of abortion, symmetrical cortical necrosis of the kidney, a probably much rarer phenomenon, has been more frequently described, no doubt because of its striking morphological characteristics and puzzling pathogenesis as indicated by Oertel's¹⁸ studies. These two apparently diverse renal lesions which result in kidney shutdown, reviewed in the light cast by the recent researches of Trueta and his collaborators,¹⁹ may have a common pathogenesis based on the mechanism of renal cortical anoxia. The diversion of the blood flow from the cortex through the "lesser circulation" or medullary by-pass is probably not so complete as to result in total ischemia but presumably a limited circulation continues

through the cortex which is sufficient for nutritional purposes but not for glomerular filtration. The pallid cortex with ischemic glomeruli and congested medulla seen in kidneys of the crush syndrome favor this explanation as the cause of the anuria. Extreme shutdown of the cortical circulation may result in bilateral cortical necrosis of the kidney, in which condition the more peripheral parts of the cortex undergo a necrotic sequestration while the deepest zone of the cortex and the entire medulla survive. In striking contrast to the occluded vessels of the outer cortex with their damaged walls and the parenchymal necrosis of this zone, the medulla is viable and the vessels forming the lesser circulation congested. Trueta and associates suggest that a constriction of the arteries in the peripheral parts of the cortex takes place in the early stages of bilateral cortical necrosis in the human being, in consequence of which the blood is denied access to the cortical pathway but makes the intrarenal circuit through the medullary by-pass.

Although this thesis of Trueta is intriguing, the postulate of Young, Bywaters, and Mallory, in which heme pigment derived from degradation of muscle or blood acts as a tubular blockade must not be forgotten. This contention Bywaters has emphasized by his statement that "a more careful clinical examination for pigments in urines is needed in the early stage . . . and a more careful pathological examination for necrotic muscle . . . and less use of shock, renal anoxia and other such catch words."

The usual causes of kidney insufficiency such as renal damage due to sulfonamides, hemoglobinuria due to quinine sensitivity, or incompatible blood transfusion can be eliminated in these cases. It is also extremely unlikely that the amount of free hemoglobin in plasma of fresh donor blood or that hemoglobin derived through intravascular hemolysis due to "hemolytic" abortifacient douches would be sufficient to cause pigment nephropathy. Rather the violent means adopted to interrupt pregnancy would be the precipitating cause of the abortion-uremic syndrome.

The true answer to the pathogenesis of this problem of oliguria following abortion may be that there is an interplay between the two factors of anoxia and heme pigment precipitation.

It was believed pertinent to stress in this contribution the complication of kidney failure which may follow an induced abortion. With an awareness of the condition and its pathogenesis, gynecologists may possibly prevent post-abortion anuria or amend and improve upon present-day treatment of septic abortions.

References

1. Bywaters, E. G. L., and Beall, D.: *Brit. M. J.* 1: 427, 1941.
2. Bywaters, E. G. L., and Dible, J. H.: *J. Path. & Bact.* 54: 11, 1942.
3. Lucké, Balduin: *Mil. Surgeon* 99: 371, 1946.
4. Maegraith, B. G., Havard, R. E.: *Lancet* 2: 213, 1946.
5. Maegraith, B. G., Havard, R. E., and Parsons, D. S.: *Lancet* 2: 293, 1945.
6. Young, J.: *Brit. M. J.* 2: 715, 1942.
7. Young, J.: *J. Obst. & Gynaec. Brit. Emp.* 49: 221, 1942.
8. Paxson, N. F., Golub, L. J., and Hunter, R. M.: *J. A. M. A.* 131: 500, 1946.
9. Bratton, A. B.: *Lancet* 1: 345, 1945.
10. Humphrey, J. H., and Jones, F. A.: *Clin. Sc.* 6: 173, 1947.
11. Fernandez, L. B., and Fromm, G. A.: *Día méd.* 18: 576, 1946.
12. Young, J., and Walker, A. H. C.: *J. Obst. & Gynaec. Brit. Emp.* 54: 196, 1947.
13. O'Sullivan, J. V., and Spitzer, W.: *J. Obst. & Gynaec. Brit. Emp.* 53: 158, 1946.
14. Schmorl: *Pathology of Eclampsia*, Leipzig, 1893, F. C. W. Vogel.
15. Brutt and Shumm: *Ztschr. f. Geburtsh. u. Gynäk.* 80: 145, 1918.
16. Mallory, Tracy, B.: *Am. J. Clin. Path.* 17: 427, 1947.
17. Rendle-Short, C.: *J. Obst. & Gynaec. Brit. Emp.* 49: 581, 1942.
18. Scriven, W. de M., and Oertel, H.: *J. Path. & Bact.* 33: 1071, 1930.
19. Trueta, J., Barclay, A. E., Franklin, K. J., Daniel, P. M., and Prichard, M. M. L.: *Studies of the Renal Circulation*, Springfield, Ill., 1947, Charles C Thomas.

A STUDY OF NATIVE SPECIES OF MALE TOADS AS TEST ANIMALS IN THE DIAGNOSIS OF EARLY HUMAN PREGNANCY*

PAUL F. MCCALLIN, M.D., AND RICHARD W. WHITEHEAD, M.A., M.D.
DENVER, COLO.

(From the Department of Physiology and Pharmacology and the Department of Obstetrics and Gynecology, University of Colorado Medical Center)

AFTER Aschheim and Zondek had placed the diagnosis of early human pregnancy on a sound scientific basis, Shapiro and Zwarenstein¹ in 1934 demonstrated that a species of amphibian, the female South African clawed toad, *Xenopus laevis*, responded to the injection of gonadotropins present in urine from pregnant women by the extrusion of eggs. Then in 1947 Galli-Mainini² used the male member of a species of South American toad, *Bufo arenarum* Hensel, in the routine diagnosis of pregnancy showing that this animal responded to the injection of pregnancy urine by the rapid release of spermatozoa via the urine. He claimed advantages over the standard rabbit and rat tests of speed, simplicity, clear end point, specificity, and economy. In another report Galli-Mainini³ summarized the results of 2,030 tests. There were no false positives. In pregnancies up to the fifth month there were 458 positive results out of 462 specimens, an accuracy of 99.01 per cent. The earliest positive result was obtained four days after the first missed period. He also mentioned that other species of South American toads could be used.

Following Galli-Mainini's first report, Wiltberger and Miller⁴ found that the male leopard frog, *Rana pipiens*, responded in a similar manner. In over 200 tests they had no errors in the first trimester of pregnancy. Robbins and Parker⁵ performed 122 tests using the male frog and obtained only one false result, a negative test in a woman two weeks past her first missed period.

The response of the South American toad to human gonadotropins interested us in the possibility that species of male toads native to Colorado would respond in a similar manner. Two species have been tested, *Bufo woodhousii* of Girard and *Bufo americanus*. *Bufo woodhousii* Girard is the most widely distributed species of toad in Colorado, being found both east and west of the mountains and in other western states from Texas north to Kansas and west of the Rockies to Nevada and eastern California. *Bufo americanus*, the common toad of North America, is found in Colorado only east of the mountains, but is generally distributed throughout North America east of the Rockies as far north as Hudson Bay.⁶

*Read before the regular meeting of the Denver Gynecological and Obstetrical Society, Dec. 6, 1948.

The male may be easily differentiated from the female in both species of toad by the presence of a dark coloration of the skin of the throat as well as a characteristic croak which the female does not possess. In the female, the throat is devoid of pigment or at most faintly speckled (Fig. 1). The development of the clasping digit of the male toad is not pronounced as in the male frog.

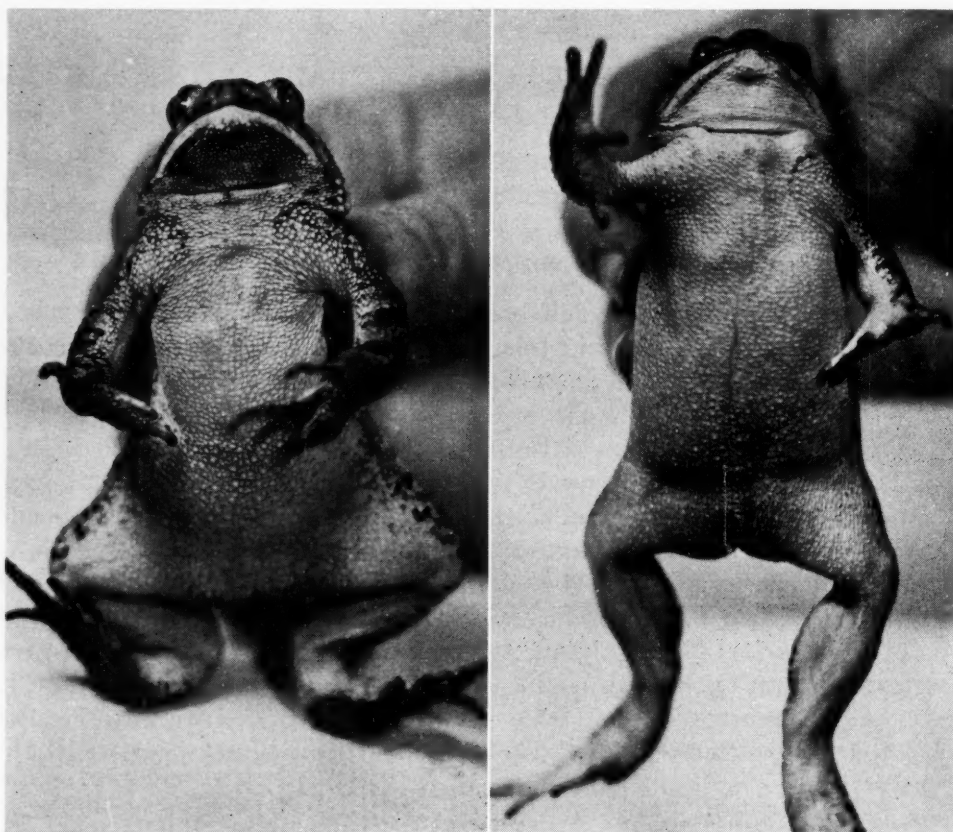


Fig. 1.—Ventral view of male (left) and female *Bufo woodhousii* Girard showing difference in throat pigmentation.

Technique

The technique of performance of this test is quite simple and requires no special training. The first morning specimen of urine is used because it is concentrated and likely to contain more gonadotropin than dilute specimens voided later in the day. Without any preparatory treatment such as filtration or adjustment of pH, 5 c.c. of urine are injected into the dorsal lymph sac of the toad. This is merely an injection under the skin of the back. Care should be taken to introduce the needle just under the skin since deeper injection may result in puncturing the lungs which the animal frequently inflates when handled.

Three hours later a specimen of toad urine is obtained by introducing the tip of a small (e.g. 1 c.c.) pipette into the cloacal orifice. A drop of urine will collect in the pipette by capillary action within a moment. The urine is then examined unstained with the low power of a microscope under reduced illumination. If the test is positive, numerous motile, threadlike spermatozoa will be present (Fig. 2). With higher magnification the spermatozoa appear as

spindle shaped, elongated heads with fine threadlike tails. If the test is negative, specimens are examined again at five and twenty-four hours. It is also our practice to examine the urine for presence of spermatozoa before using the toads though none have been found prior to injection. Spermatozoa persist twenty-four to forty-eight hours but it is best not to use the animals again at less than weekly intervals. Injecting animals every four days, we have found that they have died following the fourth injection. This does not occur when a rest period of one week is allowed.

Occasionally an animal will die either from toxic substances in the urine or as a result of puncturing the lung following too deep an injection. In our series five animals have been lost in this manner. If death is due to toxic substances in the urine, the specimen may be detoxified by shaking it with an equal amount of ether.

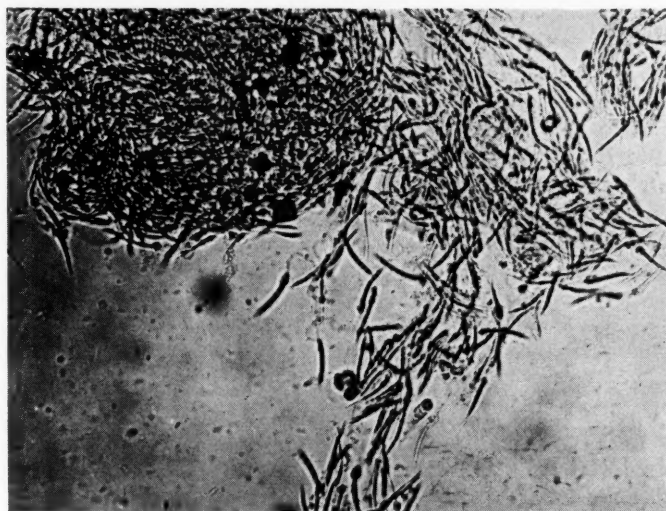


Fig. 2.—Toad spermatozoa, unstained. ($\times 175$.)

Results

We have performed a total of 168 tests to this date. Five animals have died as a result of the injection; two died, however, in determining that the rest period must be longer than four days. There were 86 negative results and 77 positive results. *In no case did nonpregnancy urine give a positive test.* Four male urines gave negative results. In two cases urine specimens from women in the sixth month of pregnancy gave negative results. Three other specimens obtained from women at this advanced stage of pregnancy gave positive results.

In 65 cases, toad tests were run on urine specimens received from another laboratory where Friedman tests had been performed. Results agreed in 64 cases. In one test, the toad gave a negative result while the Friedman test was positive. The patient could not be followed to ascertain which was correct. Four specimens were tested on which Aschheim-Zondek tests had been performed. In all four cases, results were identical. Remaining tests were performed on specimens obtained from patients seen in the Colorado General Hospital Outpatient Department who were suspected of early pregnancy. All results in these cases were proved correct by clinical follow-up. The earliest positive result was obtained only eight days after the first missed menstrual period. Two ectopic pregnancies were included in the series, and both cases gave positive results.

Urine specimens from two patients with hydatidiform moles were tested. Both gave positive results in dilutions of 0.05 c.c. Basing our calculation on the observation that these toads have responded to a minimum of 10 rat units of a commercial preparation of chorionic gonadotropin, we estimated that there were at least 200,000 rat units of gonadotropin per liter in these specimens, a level consistent with the diagnosis of mole.

Toads have been injected up to twelve times with no apparent decrease in accuracy. One effect of repeated injections seems to be an occasional slowing of reaction time. On the first injection all positive results were evident within three hours. However, on further injection, spermatozoa did not appear until five hours in nine positive tests and until 24 hours in four such tests out of a total of 62 positive results in animals injected more than once. *Bufo americanus* was used in eighteen tests and *Bufo woodhousii* Girard in the remaining 150 tests. Of the two false negatives in women six months pregnant, one occurred in each species. The result in disagreement with that of the Friedman test was obtained in *Bufo woodhousii* Girard.

Discussion

The results in this series demonstrate that male toads common to Colorado and North America east of the Rockies react to the injection of human pregnancy urine in a manner similar to South American toads and the frog, *Rana pipiens*. These animals would seem to offer a practical means of testing for early pregnancy. Important is the fact that no false positives were obtained. The three apparent false negatives merit further discussion.

In the two tests of urine specimens from the sixth month of pregnancy, the negative results were obviously in error. However, at this time, clinical signs are present that would not require a laboratory test for diagnosis. Browne and Venning,⁷ using rats in assaying gonadotropin levels, have shown that after the third month of gestation urinary excretion of gonadotropin is at a low level, ranging from 1,500 to 5,000 rat units (R.U.) per liter for the remainder of the pregnancy. If 1,500 R.U. per liter were present in the specimen, 5 c.c. of urine would contain only 7.5 R.U. Our animals have not responded to less than 10 R.U. of chorionic gonadotropin. Galli-Mainini³ reported a fall in accuracy from 99.01 per cent to 92 per cent after the fifth month using the South American toad. Wiltberger and Miller,⁴ using frogs, reported 50 per cent false negatives in the last trimester of pregnancy.

As to the one discrepancy between the negative toad test and positive Friedman test in which the result could not be confirmed by following the patient, three possibilities exist. This test was performed in an animal that had been used twice previously. At that time, it was not realized that repeated use of the toads may slow the appearance of spermatozoa. Thus by not observing the animal at twenty-four hours, a positive result may have been missed. Second, the Friedman test may have been in error. Galli-Mainini³ reported that in 312 Friedman and toad tests performed coincidentally, nineteen discrepancies occurred. In the follow-up of these nineteen patients, it was proved that the toad test was correct in seventeen cases and the Friedman in two cases.

These native toads offer several advantages as test animals for early pregnancy. The animals are readily obtained locally in small numbers or in unlimited numbers from biological supply houses at about a dollar a dozen. The toads are hardy animals and are easily kept in a wooden box with some earth and a small pan of water. They do not require protection from drying with water-filled tanks as do frogs. Feeding is required only once every ten to fourteen days, or not at all if the animals are kept for only two to three months. Any live insect or worm is taken readily. We have found it more convenient to force feed the animals with small pieces of meat.

Laboratories running only a few tests and rural physicians could easily keep a few animals, using them repeatedly as required. The simplicity and speed of the test as described are evident, and it is clearly possible to perform it as an office procedure.

Our animals have not been used during the spring breeding season, but Galli-Mainini did not find any interference with results in *Bufo arenarum* Hensel if the males were isolated from the females at this time.³

Summary

This study demonstrates that the native male toads, *Bufo woodhousii* Girard and *Bufo americanus*, respond to the injection of pregnancy urine by the rapid release of spermatozoa.

Other studies using South American toads and the frog, *Rana pipiens*, seem to indicate that this response is generalized in those toads and frogs having a continuous spermatogenesis.

In 168 tests performed, no false positives were obtained. Two false negatives were noted in late pregnancy. In 69 Friedman or Aschheim-Zondek and toad tests performed coincidentally, one discrepancy occurred. The result could not be checked by a follow-up of the patient.

Toads are hardy, economically obtained, easily kept, and may be used repeatedly as test animals.

The simplicity and rapidity of the test allow its use as an office procedure.

We wish to thank Drs. A. W. Freshman and S. K. Kurland for their cooperation in furnishing urine specimens on which Friedman tests had been performed in their laboratory.

We are indebted to Chalmers J. Rayburn for technical assistance.

References

1. Shapiro, H. A., and Zwarenstein, H.: *Nature* 133: 762, 1934.
2. Galli-Mainini, C.: *J. Clin. Endocrinol.* 7: 653, 1947.
3. Galli-Mainini, C.: *J. A. M. A.* 138: 121, 1948.
4. Wiltberger, P. B., and Miller, D. F.: *Science* 107: 198, 1948.
5. Robbins, S. L., and Parker, F.: *Endocrinology* 42: 237, 1948.
6. Cockerell, T. D. A.: *Zoology of Colorado*, Boulder, Colo., 1927, University of Colorado Press.
7. Browne, J. S. L., and Venning, E. M.: *Lancet* 2: 1507, 1936.

Galli Mainini, Carlos: *Pregnancy Test Using the Male Batrachia*, *J. A. M. A.* 138: 221, 1948.

The accuracy of the test was verified in 1,422 cases of suspected pregnancy; in 960 instances the patient was not pregnant and negative results were obtained in all. In 462 cases of verified pregnancy, positive results were obtained in 458 (99.01 per cent accuracy). It is shown that 89 per cent of the positive reactions occur within the first twenty-four hours after the injection is given. With urine of nonpregnant individuals the results were 100 per cent accurate. A lower incidence of positive reactions was obtained in pregnancies between the sixth and the ninth month. The same toad can be used again after an interval of one week.

Gonadotropic administration stimulates the interstitial cells and spermatogenesis and produces detachment of spermatozoa from the Sertoli cells. Free spermatozoa migrate to the bladder and can be obtained by means of a pipette introduced into the cloaca.

WILLIAM BERMAN,

USE OF THE MALE FROG (*RANA PAPIENS*) IN A BIOLOGICAL PREGNANCY TEST

HERMAN L. GARDNER, M.D., AND NANCY B. HARRIS, B.S., R.N.,
HOUSTON, TEXAS

(From the Department of Gynecology, Baylor College of Medicine,
and the Texas Medical Center)

SINCE the introduction of the Aschheim-Zondek test¹ in 1928, and the Friedman test² in 1931, numerous biological, chemical, and skin tests for pregnancy have been described, but few have proved sufficiently practical or accurate to gain acceptance. Not until the introduction by Shapiro,³ in 1933, of the female South African clawed frog (*Xenopus laevis*), did any of these tests approach the reliability of the Aschheim-Zondek and Friedman tests. Female frogs have not been widely used because they have not been readily available, and because the gonadotrophins must be extracted from relatively large volumes of urine by a rather difficult chemical procedure. Shapiro's work demonstrated that the ovaries of Amphibia will respond to the gonadotrophins of human pregnancy urine. In 1947, Robbins and Parker⁶ showed that the male South African clawed frog (*Xenopus laevis*) could be made to excrete spermatozoa by the injection of gonadotrophic hormones.

The introduction by Mainini⁴ in March, 1947, of a frog test using the male South American frog (*Bufo arenarum* Hensel) has apparently marked the beginning of a new era in biological pregnancy tests. Both his original⁴ and recent⁵ works have shown that this male South American frog, when injected with human pregnancy urine, will excrete spermatozoa, and that such reaction is a highly accurate, rapid, and simple means of diagnosing pregnancy. He obtained over 98 per cent accuracy in over 2,000 tests. A false positive test was not encountered during his extensive study, which included several hundred urines of nonpregnant subjects.

Wiltberger and Miller⁷ in February, 1948, reported on the use of the male North American frog (*Rana pipiens*) as a test animal for pregnancy. Their method was to inject 5 c.c. of suspected urine and examine microscopically the frog's urine for spermatozoa. They reported excellent results in early pregnancy, but 50 per cent false negatives in the last trimester. There were no false positives in their series.

Robbins and Parker,⁸ also using the North American frog (*Rana pipiens*), performed 112 tests, and of 78 known pregnancy urines, 77 were positive. No false positives were reported.

Since completion of the present study, Brody¹⁰ has published his experiences with the *Rana pipiens*, in which 55 urines were correctly positive, 11 falsely negative, and 48 correctly negative.

Physiological Basis for Test

The frog testicle is an elongated structure attached to the dorsal side of the peritoneal cavity. The organs are attached to the kidney of the same side by a ligament through which pass collecting tubes which carry spermatozoa. These

tubes empty into kidney glomeruli. The kidney tubules, ureters, and bladder are thus common excretory channels for both urine and spermatozoa. This arrangement allows for external fecundation, which is natural with the frog.

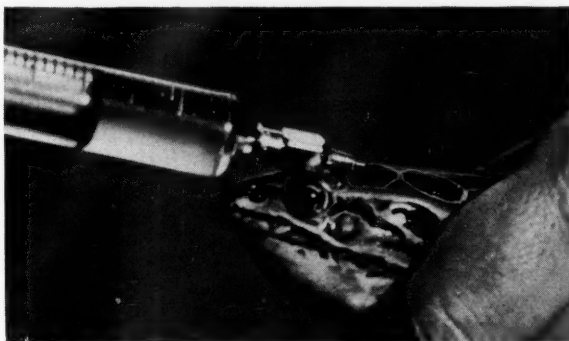


Fig. 1.—A method of holding and injecting urine to be tested.

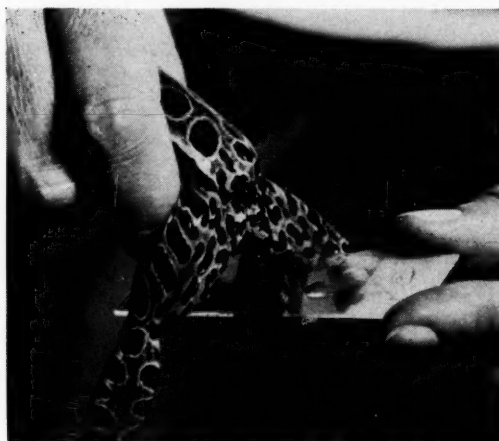


Fig. 2.—A method of expressing urine from the frog.

The gonadotrophic hormones contained in the urine of pregnant women, when injected into a frog, are capable of causing a detachment and excretion of previously formed spermatozoa. Spermatogenesis is also probably stimulated by these urinary gonadotrophins, but it is the former action which explains the rapidity with which spermatozoa are found in the frog's urine following injection with pregnancy urine. It is probable that frogs excrete spermatozoa only after stimulating doses of gonadotrophic hormones, or after riding and embracing the ovulating female. There is apparently no ovulating and mating under ordinary laboratory conditions. As a control, twelve healthy male and twelve healthy female frogs were kept in the same container, at room temperature, during the month of July. Daily urine examinations from the male frogs were made for two weeks, but no urine showed the presence of spermatozoa, and there were no signs of ovulation. From available information, the evidence is that the adult male *Rana pipiens* possesses preformed spermatozoa in the testicle during all seasons, and it further seems evident that these spermatozoa can be liberated by adequate amounts of pregnancy urine gonadotrophins.

Material and Method

The frogs used in this study were *Rana pipiens*, also known as the North American green frog, or grass frog. They are the frogs commonly used in physiology laboratories in this country. The average weight of the frogs used was 50 grams, and this was fairly uniform. The urine to be tested was filtered through ordinary filter paper. Two and one-half c.c. were injected subcutaneously into the dorsal lymph space of each of two frogs. The frogs' urines were examined at the end of one hour for the presence of spermatozoa. If none were found, an additional 2.5 c.c. of urine were injected. The split dosage method was used because of the higher frog mortality rate when 5 c.c. were injected as a single dose. The frogs' urines were examined again at two hours and four hours from the time of the first injection. A method of holding the frog for injection, and a method of pressing urine from the frog are shown in Figs. 1 and 2. The urine can also be collected in a beaker, and transferred to a glass slide with an eye dropper. The frog's urine is then covered with a cover slip. The slide is examined under low power, using a markedly subdued light. The high power is occasionally used for more definite recognition of isolated spermatozoa. All specimens were called positive if one or more spermatozoa, motile or nonmotile, were found.

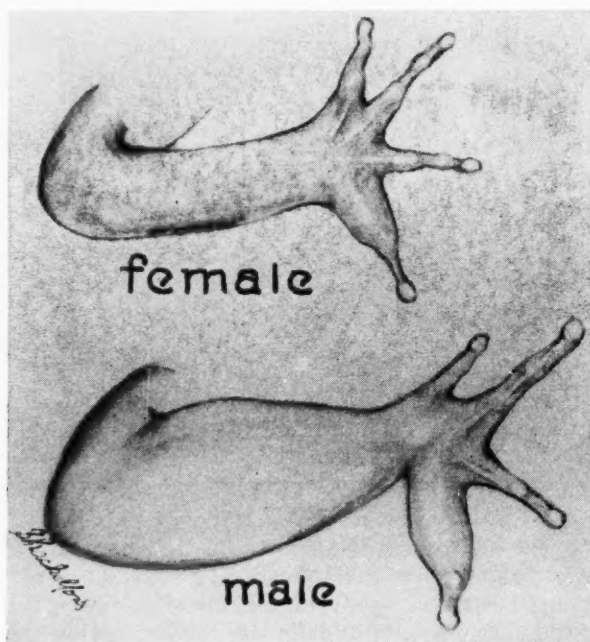


Fig. 3.—Recognition of the male and female frog. The male has more muscular forearm and thumb.

A total of 343 individual urine specimens were examined. Two hundred fifty-six of these were from 142 women known to be, or who subsequently proved to be, pregnant; 60 were from women known not to be pregnant, or who subsequently proved not to be pregnant, and 27 were from a special group of six women, two of whom had tubal pregnancies, and four of whom had hydatidiform moles.

Recognition of the Male Frog

The frog has no external sexual organs, but certain secondary sexual characteristics make recognition of the male and female easy. The male has a

thicker and slightly darker thumb, and its forearm is larger and more muscular (Fig. 3). The male will sometimes croak when picked up. There are other minor but less definite morphological differences.

Morphology of the Frog's Spermatozoa

The spermatozoa (Figs. 4 and 5) of the *Rana pipiens* are considerably larger than human spermatozoa. The heads are cylindrical, or cigar shaped, instead of pear shaped. The tails are much thinner, and are hardly visible in the nonmotile cell. They are less actively motile than human spermatozoa. They appear singly, or in groups or clusters.

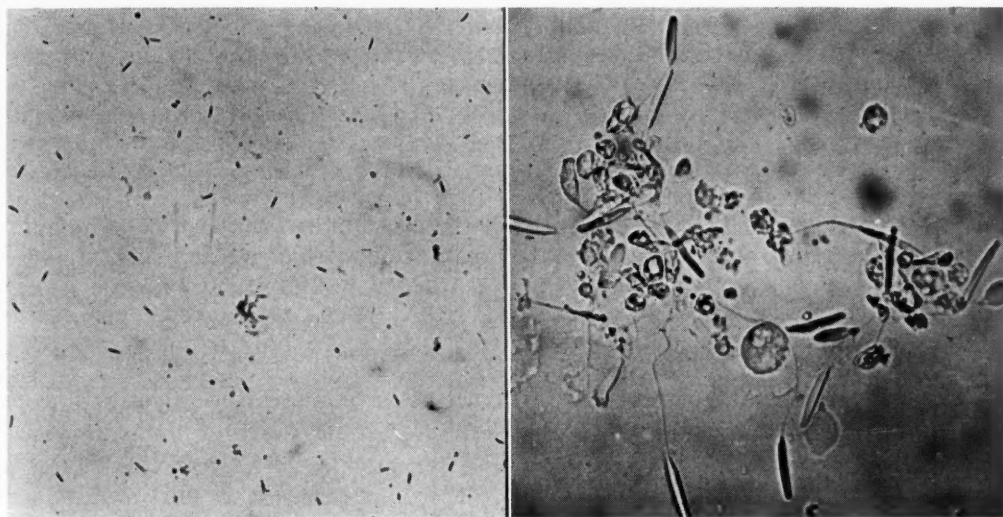


Fig. 4.

Fig. 4.—Low power of frog's spermatozoa.

Fig. 5.

Fig. 5.—High power of frog's spermatozoa.

Analysis of Results From the Known Pregnant Group

A total of 256 urine specimens were examined from a group of women known to be, or subsequently proved to be, pregnant. These 256 urines were collected from a total of 142 patients. The results are tabulated as follows:

23 specimens—	5 to 8 weeks' amenorrhea—	20 or 87 % positive
33 specimens—	8 to 12 weeks' amenorrhea—	30 or 90.9% positive
41 specimens—	12 to 16 weeks' amenorrhea—	27 or 65.9% positive
62 specimens—	16 to 20 weeks' amenorrhea—	22 or 35.5% positive
44 specimens—	20 to 24 weeks' amenorrhea—	20 or 45.4% positive
25 specimens—	24 to 28 weeks' amenorrhea—	13 or 52 % positive
28 specimens—	28 to 40 weeks' amenorrhea—	12 or 42.9% positive

As indicated from the figures above, of a total of 256 specimens examined from women of known pregnancy, 144 were positive. This gives an over-all correct positive reaction of 56.3 per cent. This is in contrast to the results obtained by Mainini,⁵ using the *Bufo arenarum* Hensel, who obtained over 98 per cent correct positives, and it is also in contrast to the work of Robbins and Parker,⁸ who used the same species of frog (*Rana pipiens*) as used in the present series. The latter workers obtained 77 positive reactions in 78 pregnancy

urines. The South American frog used by Mainini is apparently very sensitive to pregnancy urine gonadotrophins. The *Rana pipiens* used by Robbins and Parker came from Vermont, and the frogs used in the present study came from Wisconsin. Robbins and Parker made no mention of the number of specimens tested during the various trimesters of pregnancy, and comparisons are hardly valid without this information. Had all of the specimens examined by them been from a group of women six to twelve weeks pregnant, the much higher percentage of positive reactions would be easily understandable. Admittedly, many of the frogs used in the present study were not in the best of health. Many could be considered old frogs, in storage over one month. We have subsequently learned that our method of storage (too cold and too wet) is not suitable to their well-being. Many of the frogs, too, had the condition known as "red leg." These factors of poor health probably lower a frog's responsiveness to gonadotrophins. In the present series, it is noted that of the 23 pregnancy urines tested from women 5 to 8 weeks amenorrheic, 87 per cent were positive. There were three false negatives, and it is of interest that all of these were specimens from the same patient, taken at 5 weeks' amenorrhea, 5½ weeks' amenorrhea, and 8 weeks' amenorrhea. This patient with three false negatives showed a positive reaction on a specimen collected at 11 weeks. The 23 urines in this group were collected from a total of 17 patients. Of the group of 33 pregnancy urines, collected from women 8 to 12 weeks amenorrheic, 90.9 per cent were positive. The percentage positives fell markedly in the 12 to 16 week group (65.9 per cent), and was lowest in the 16 to 20 week group (35.5 per cent). After the 20th week, positives were fairly uniform, near 50 per cent, and this was the experience of Wiltberger and Miller.⁷

In plotting a curve of percentage correct positives against weeks of gestation, a graph is seen which corresponds closely to the gonadotrophic curve in pregnancy, as was determined by Siegler and Fein.⁹ This, too, was the observation of Wiltberger and Miller.⁷

Speed of Reaction

Of the 144 correct positive reactions, 106, or 73.6 per cent, were positive at the end of one hour, and this was after only 2.5 c.c. of urine; 29, or 20.2 per cent, became positive at the end of two hours, and 9, or 6.2 per cent, became positive at the end of four hours. These figures seem to indicate that only a few, at most, additional positive tests would have been found by making subsequent examinations of the frogs' urines.

Relationship of Positivity to Specific Gravity

229 pregnancy urines, from all periods of gestation, were tested for specific gravity, and the results were:

Specific gravities 1.001 to 1.009	51 specimens	18 or 35.3% positive
Specific gravities 1.010 to 1.019	124 specimens	71 or 57.3% positive
Specific gravities 1.020 to 1.030	54 specimens	37 or 68.5% positive

Only a glance at this table shows a positive relationship between specific gravity and positivity.

Relationship of Early Morning Specimens to Positivity and Specific Gravity

Of the 229 known pregnancy urines tested for specific gravity, 186 were considered to be early morning specimens. These showed an average specific gravity of 1.013, while 43 non-morning specimens showed an average specific gravity of 1.015. Since early morning specimens are usually thought of as having higher specific gravities, the findings here seem paradoxical and not easily ex-

plained. Although the early morning specimens showed a slightly lower average specific gravity, 104, or 55.9 per cent, were positive, as compared to the non-morning specimens, in which 22, or 51.2 per cent, were positive. The number of non-morning specimens (43) is too small for the comparison to be of real value or to warrant conclusions. The study on specific gravities has shown a parallel relationship between urinary concentration and positivity, while it has failed to show any overwhelming advantage to early morning specimens.

Duration of Positive Reaction in Injected Frogs

A sufficient number of frogs were still positive after seven days to preclude the possibility of their re-use at the end of this time. This has not been the experience of others. Further investigation is needed.

How Long Will Urine Remain Positive?

The urine from a woman with an ectopic pregnancy was kept for two weeks, at room temperature, and was still found strongly positive at the end of this time. Several specimens were examined after standing, at room temperature, for five or more days, and were still found to be positive.

False Positive

Of 60 tests done on women considered not to be pregnant, or who subsequently proved not to be pregnant, one showed a definite positive reaction in each of two frogs. These frogs were fresh and had not been previously used. The patient had been amenorrheic for forty days, and her physician, on the assumption that she was pregnant, administered relatively large doses of stilbestrol with the idea of preventing an abortion. The significance of the stilbestrol, if any, to the false positive reaction cannot be explained. After the patient's uterus failed to enlarge, stilbestrol was stopped and menstruation occurred within a few days. No objective evidence of pregnancy was ever present, and a subsequent frog test, after cessation of menstruation, was negative.

Ectopic Pregnancy

Urines were tested from two women suspected of having tubal pregnancies:

Mrs. R. R. had tests at 7 and 8 weeks, following her last normal menstrual period, both of which were negative. A test at 10 weeks showed a positive reaction in both frogs. At operation, a tubal pregnancy was found in situ. The tubal mass was 4 cm. in diameter. No fetal sac or fetus was present. Only a few villi were seen on microscopic examination.

Mrs. B. M. was 7 weeks past her last menstrual period. A morning specimen was strongly positive in both frogs. Operation was performed and a tubal pregnancy, with early rupture, was found. The urine from the patient in this case, after standing at room temperature for two weeks, still gave a strongly positive reaction in each of two frogs.

Hydatidiform Mole

Tests were run on the urines of four women who proved to have hydatidiform moles by both gross and microscopic examinations. No fractional tests were run.

Mrs. R. L.: First test performed 12 weeks after last normal menstrual period. This was before the patient was known to have a mole. Reaction was strongly positive. Tests at 15 and 16 weeks were also strongly positive. The uterus failed to enlarge, remaining the size of a two months' pregnancy. Four days following a curettage, a test was weakly positive. Four additional tests up to three weeks following curettage were negative.

Mrs. L. V.: Two specimens of urine were examined, one two days, and one 16 days after the patient had passed a mole. Both tests were strongly positive in each frog. There were no further studies.

Mrs. M. F.: On the day that a large volume of mole was passed, a test was weakly positive. A curettage was done on this day. Ten tests were run during the following 21 days, and all were negative.

Mrs. H. H.: A mole was passed four months after the last normal menstrual period. One day after the mole was passed, a test was strongly positive. There were no follow-up studies.

Discussion

Pregnancy tests, using the North American frog (*Rana pipiens*), have given a correct positive reaction in 89.5 per cent of cases in the first trimester of pregnancy; whereas, in the last two trimesters, an over-all percentage of correct positive reactions was obtained in only 47 per cent. The latter figure of low percentage correct positive reactions should not be too discouraging, since it is not during the second and third trimesters that one relies on biological pregnancy tests for a differential diagnosis.

The experience of this study and the experiences of others indicate that a positive reaction is almost 100 per cent reliable. Since false positive tests must be rare, and thus of no great concern, it seems logical that a greater volume of suspected urine could be injected to eliminate possibly many of the false negative reactions. The mortality rate for the frogs would probably be high if more than 5 c.c. of untreated urine were injected. The development of a simple method of detoxifying urine would be of great advantage, or possibly as good would be a simple method of concentrating the gonadotrophins. Brody¹⁰ used larger volumes of urine, but, before injection, detoxified and concentrated the specimens to be tested by a method using "Adsormone." The method is certainly not one of real simplicity. When this problem has been worked out, it seems likely that the high percentage of false negative reactions can be lowered, while at the same time, it is not likely that the correct negatives will be changed.

Other possible solutions for eliminating the numerous false negatives suggest themselves: the discovery or development of a more sensitive *Rana pipiens*; availability of the frog, *Bufo arenarum* Hensel, used so successfully by Mainini⁵; use of only fresh and healthy frogs, and frogs which have been properly stored.

It seems reasonable to assume that the male frog test for pregnancy will find a usefulness approaching that of the Friedman and Aschheim-Zondek tests. It is potentially a test of high accuracy, one which is extremely rapid, and one which is inexpensive and technically easy. The minor problems yet to be solved are not likely to prove difficult.

Summary

1. A total of 343 urine specimens were examined.
2. Of 256 pregnancy urines examined, 144, or 56.3 per cent, were positive, meaning that 43.7 per cent were falsely negative.
3. Of 60 urines from nonpregnant women, 59, or 98.3 per cent, were correctly negative, while one was falsely positive.
4. Of 144 positive reactions in the known normally pregnant group, 106, or 73.6 per cent, were positive at the end of one hour, and this was with 2.5 c.c. of urine.

5. A definite relationship between specific gravity and positivity is shown.
6. The average specific gravity of 186 supposedly early morning specimens of pregnancy urine was 1.013, while the average specific gravity of 43 supposedly non-morning specimens of pregnancy urine was 1.015.
7. 55.9 per cent of 186 supposedly early morning specimens of pregnancy urine were correctly positive, while 51.2 per cent of 43 supposedly non-early morning specimens of pregnancy urine were correctly positive.
8. It has been shown that pregnancy urines remain positive for several days after standing at room temperature, and this is without a preservative.
9. Of the frogs tested with pregnancy urine, an occasional one showed one or more spermatozoa in its urine after seven days.
10. The urines of two women with ectopic pregnancy were tested and found positive.
11. The urines of four women with hydatidiform moles were tested and all found positive.

Addendum

Since this paper was submitted for publication, additional articles^{11, 12, 13, 14} have come to our attention. We have made no search of recent literature, so we apologize to any author who may have published an article not included in the references.

Since completion of the work in the above analysis (August, 1949) 52 additional urines have been examined from private patients of the senior author, and Dr. Thomas G. Gready, Jr. Each of these 52 tests was done for aiding a diagnosis. It is probable that only from such a group can the true worth of the test be evaluated. Of the 52 tests run, 20 were correctly positive, 21 were correctly negative, and 11 were falsely negative. Of these 11 falsely negative tests, two subsequently aborted blighted ova, and the majority of the remaining nine were within six weeks of a last menstrual period.

It can be further concluded that an inadequate amount of urine is being injected into the frogs, and this speaks for the desirability of a simple method of concentrating or detoxifying urine to be tested. As yet, a really simple method has not been described. Instead of concentrating all specimens to be tested, as has been proposed by Cutler,¹³ it seems more practical to concentrate only those specimens which fail to give a positive result with the natural specimen.

Since we have learned a better method of storing the frogs, a higher percentage of correct reactions is being obtained. We are using a covered enameled refrigerator pan, into which is placed one or two inches of peat moss. The peat moss is made wet with distilled water, and a small excess of water is kept in the bottom of the pan. This pan is kept in the refrigerator at about 40° F. In this environment the frogs have remained healthy and free from "red leg," and the evidence is that a healthy frog is more responsive to pregnancy urine.

References

1. Aschheim, S., and Zondek, B.: *Klin. Wehnschr.* 7: 8, 1928.
2. Friedman, M. H., and Lapham, M. E.: *AM. J. OBST. & GYNEC.* 21: 405, 1931.
3. Shapiro, H. A., and Zwavenstein, H. A.: *Tr. Roy. Soc. South Africa* 22: (Univ. of Proc., 75, Oct. 18, 1933) 1934.
4. Mainini, C. G.: *Semana méd.* 54: 337, 1947.
5. Mainini, C. G.: *J. A. M. A.* 138: 121, 1948.
6. Robbins, S. L., Parker, F., Jr., and Bianco, P. D.: *Endocrinology* 40: 227, 1947.
7. Wiltberger, P. B., and Miller, D. F.: *Science* 107: 198, 1948.
8. Robbins, S. L., and Parker, F., Jr.: *Endocrinology* 42: 237, 1948.

9. Siegler, S. L., and Fein, M. J.: AM. J. OBST. & GYNEC. 38: 1021, 1939.
10. Brody, Henry: AM. J. OBST. & GYNEC. 57: 581, 1949.
11. Miller, D. F., and Wiltberger, P. B.: Ohio J. Science 48: 89, 1948.
12. Pickett, Robert F., Wiltberger, P. B., and Miller, D. F.: Ohio J. Science 48: 246, 1948.
13. Cutler, J. N.: J. Lab. & Clin. Med. 34: 554, 1949.
14. Soucy, Leonide B.: Am. J. M. Technol. 15: 184, 1949.

Farris, Edmond J.: Temperature Compared With Rat Test for Prediction of Human Ovulation, J. A. M. A. 138: 560, 1948.

The author reports observations made on 27 women using the rat test as described and comparing it with the basal body temperature curve. Twenty-three of the 27 women had their ovulation timed during the month that conception occurred. Sixteen of the women became pregnant by coitus and 9 by single inseminations—four by anonymous donors and five by homologous donors. By comparison with the basal body temperature, the records presented in this series revealed that from 2 to 15 days were required for the rising temperature to reach its highest point. The majority, or 59 per cent, of the temperature rises required four or more days. The temperature rise was abrupt in only one subject. The cycles averaged twenty-four to thirty-four days in length. Conceptions occurred on cycle days 9 to 17, inclusive. The time elapsing between ovulation and menses (postovulatory interval) during the months before the one in which conception occurred averaged fourteen and seven-tenths days, with a range of from eleven to seventeen days. These figures indicate that at least 41 per cent of the conceptions took place before there was any change in temperature. Thirty-seven per cent were interpreted as occurring as the temperature was rising; 15 per cent of the subjects conceived when their temperatures were at the lowest point, and in 7 per cent conception took place after the rise. The use of the basal body temperature as a method for detecting the time of ovulation may serve as an aid in the treatment of infertility in women in about 45 per cent of the cases. It is not a satisfactory method for detecting the day of ovulation of all patients.

WILLIAM BERMAN.

Siddall, R. S., and Mack, H. C.: Primary Endometriosis of the Cervix Uteri, Harper Hosp. Bull. 7: 195, 1949.

In a review of the literature the authors found only six cases of certain or probable primary endometriosis of the cervix uteri. However, in the last nine years, they have seen four cases in their private practice and one case in the Harper Hospital clinic, in which the diagnosis of primary endometriosis of the cervix was made. In the authors' five cases the endometrial lesions were on the anterior lip of the cervix in four cases (with an additional lesion of the posterior lip in one instance), and in one case there was a small endometrial lesion in an incision scar of the cervix. There was no evidence of extension from endometriosis of the uterus, rectovaginal septum, or vaginal wall. The number of cases seen by the authors in their own practice, compared with the number of cases recorded in the literature, suggests that primary endometriosis of the cervix is much more common than indicated in the literature. In the cases reported and in the authors' own cases, abnormal vaginal bleeding was the most common symptom; pain was not a predominant symptom. Clinically endometriosis of the cervix shows some resemblance to carcinoma; differential diagnosis is made by tissue biopsy. The endometrial lesion can be excised or destroyed with the cautery. Whether endometriosis plays a role in the origin of adenocarcinoma of the cervix is unknown.

HARVEY B. MATTHEWS.

THE USE OF MONOZYGOUS AND DIZYGOU TWINS IN THE STUDY OF HUMAN HEREDITY

MADGE T. MACKLIN, M.D., COLUMBUS, OHIO

(From the Departments of Medicine and Zoology, Ohio State University)

TWINS are an important tool which the student in human heredity can use for elucidating certain problems in his field. In order that the fullest value may be extracted from a study of twins, it is desirable to know, if possible, whether they are from one egg or two, that is, whether they are identical or fraternal twins. The obstetrician is the first member of the medical profession to come into contact with twins, and it is often upon his statement as to whether the twins are identical or fraternal that the human geneticist must rely. It is essential, therefore, that the obstetrician should know some of the fundamental rules about diagnosing the type of twins. If he sees how the knowledge is to be used, and what it can contribute, he may be more eager to furnish correct data.

We believe that sex is genetically determined, hence, that no pair of identical twins will be of the male-female, or MF type. All identical twin pairs will be either MM (two males) or FF (two females). Again, we have evidence that, when two fetuses are joined, or when they exist in the same amniotic sac with no intervening membranes, even though they are not joined, they are always of the same sex and are identical twins. Imagine, therefore, the importance of an observation of Pickering in England, which, if true, would cause us completely to revise our ideas either about inheritance of sex, or about the development of membranes in the human fetus. He reported the delivery of a pair of twins, male and female, who had two placentas, but between whom *there was no intervening membrane, and no evidence on the fetal side of the placenta that there had ever been one*. The explanation of his findings probably is that he was mistaken. The placenta should have been saved to check the accuracy of the observation.

Conditions of Membranes in Identical and Fraternal Twins

It is upon the condition of the membranes that the obstetrician usually makes his diagnosis of identical or fraternal twins to be referred to hereafter as IT and FT. He should understand just how reliable this information is. First, unequivocal evidence as to the type of twinning is given by inspection of the membranes *only when the twins are in the same amniotic sac, with no intervening membrane between them*. They may be joined together, or separate under such circumstances, but it is certain that they came from one egg. Under all other circumstances mere gross inspection of the membranes does not give a definite answer to the question of whether the twins are identical or fraternal.

If the twins are of opposite sex, of course, we are certain that they came from two eggs. Following is a series of statements about twins which may prove useful.

- | | |
|---|--|
| 1. If sex is the same | twins may be identical or they may be fraternal. |
| If sex is opposite | twins are fraternal. |
| 2. If twins are joined or are in same sac with no partition between | twins are identical. |
| 3. If a partition exists between twins they are | (a) identical if partition consists only of two amnions; or
(b) either identical or fraternal if it consists of two amnions and two chorions. |
| 4. If there is but one placenta | twins are identical. |
| 5. If there are two placentas | twins may be identical or fraternal. |

From the foregoing it is evident that dichorionic membranes or two placentas are not reliable evidence that the twins are fraternal. If the egg splits into two parts early in development, IT may have two placentas and two chorions. Furthermore, when there is a partition between the twins, microscopic examination is essential to determine whether that partition is made of four sheets of cells arranged in two layers, or whether it is made of eight sheets of cells arranged in four layers. If the first is the true state of affairs, it indicates that the partition consists of two layers of amnion only and that the twins are identical. If the second condition exists it may be that the twins are either identical or fraternal, inasmuch as there are two chorions present. We do not know what proportion of dichorionic twins are identical. Two chorions indicate two placentas and the presence of two placentas is, therefore, not a reliable guide to the type of twins. Again, one must be sure, when only *one* placenta *appears* to be present, that there is actually only one; two sites of implantation may have been so close together that the two placentas have fused and appear to be one.

Significance of Concordance and Discordance in Twins

Twins are said to be concordant with respect to a trait (and will be referred to as CT) when both twins either possess it or lack it. They are discordant (DT) when one member of the pair shows the trait and the second does not. Although the value of twins in human genetic research has been appreciated for some time, some of the relationships of concordance and discordance in twins are not understood by the average physician. Two common misconceptions are as follows: (1) if twins are discordant with respect to a given hereditary trait, it means that they are not identical; and (2) if twins are concordant with respect to a given hereditary trait they cannot be fraternal; in other words, concordance is always found in IT and never in FT. Both ideas are erroneous. For example, referring to point two, both FT will exhibit a given hereditary trait if the genetic constitution of the parents is such that they cannot do otherwise. Both fraternal Chinese twins display black straight hair and the epicanthic fold as often as will identical Chinese twins, inasmuch as these traits are universal in the Chinese population. If both parents are blood group O, all the children of the family, whether born singly, or as FT, or IT, will be of blood group O.

The first statement above is also incorrect under some circumstances although correct in others. If sex is the trait under discussion, discordance in the twins indicates that they are not identical. If, on the other hand, one is considering diabetes, in which the person possessing the gene for diabetes does not always show the disease, it is very possible to have IT discordant, one showing

diabetes and the other not. Also if the trait is one which takes time to develop, instead of being present at birth, IT may be discordant at one time in their lives, although concordant some time later, when the second twin, also, manifests the trait.

Another aspect of the above misconceptions is that if IT are discordant, or if FT are concordant, the trait is not hereditary. These two ideas are as false as the ones stated above. Hereditary traits in which the gene is not always fully penetrant (that is, not everyone possessing the gene for the trait exhibits it as an evident condition) will occur in one IT without being present in the other member of the twin pair. Also sex, which we know to be hereditary, exhibits concordance half the time in FT; hence, concordance in FT does not exclude the idea that the trait is hereditary. Actually, we should expect to find both members of an FT pair displaying concordance with the same relative frequency that we find two sibs in the same family showing the trait, even when they are not twins.

Proportions and Sex Ratios of Twin Pairs in the Twin Population

IT are always of the same sex, either pairs of males, or females. FT, on the other hand, may be both males, both females, or one twin may be male the other female. Half of FT pairs are like-sexed twins and half are unlike-sexed twins. IT form about one-third of the twin population, the remaining two-thirds being FT. If IT form one-third of the twin population, it is obvious that like-sexed twins form two-thirds, and unlike-sexed twins, one-third of all twins.

TABLE I

PROPORTION OF ALL TWINS FORMED BY		CT OR LIKE SEX	DT OR UNLIKE SEX
FT	$\frac{2}{3}$ of which $\frac{1}{2}$ are like sexed, making of which $\frac{1}{2}$ are unlike sexed, making	$\frac{1}{3}$	$\frac{1}{3}$
IT	$\frac{1}{3}$ all of which are like sexed, making	$\frac{1}{3}$	
Total		$\frac{2}{3}$	$\frac{1}{3}$

If we select a twin population made up of twin pairs in which one or both members of the twin pair exhibit a given trait, and treat this as an affected twin population, we find the above proportions altered. All twin pairs in which neither twin shows the trait are excluded from the study. As an example, we may take maleness as the trait for study. All twin pairs that are FF will be excluded, only those that are MM and MF will be selected.

TABLE II. TWIN PAIRS SELECTED FOR TRAIT OF MALENESS

PROPORTION OF ALL TWINS FORMED BY		CT OR MM PAIRS	DT OR MF PAIRS
FT	$\frac{2}{3}$ ($\frac{1}{4}$ will be MM) ($\frac{1}{2}$ will be MF)	$\frac{1}{6}$	$\frac{1}{3}$
IT	$\frac{1}{3}$ ($\frac{1}{2}$ will be MM)	$\frac{1}{6}$	
Total		$\frac{1}{3}$	$\frac{1}{3}$

Whereas, in the general twin population listed in Table I, two-thirds of the twin pairs were in the CT group, only $\frac{1}{2}$ of the twin pairs in the affected twin population are CT. The proportion of IT in the affected twin population has also dropped from $\frac{1}{3}$ in the general twin population to $\frac{1}{4}$ in the affected twin population.

A. Twin Ratios Influenced by Nongenetic, Prenatal Factors.—If some environment, external to the fetus, such as hormonal imbalance in the maternal blood stream, emotional upsets in the mother, dietary deficiencies, etc. can cause abnormal development in the fetus, such environment should affect all the con-

tents of the uterus equally, whether it be a single fetus, or twin fetuses of either fraternal or identical constitution. Hence all twins born after exposure to such environment should exhibit concordance with respect to the abnormal development. If one were to collect an affected twin population in which at least one twin exhibited the trait, one should find that all pairs were concordant, there should be no discordant pairs, with one affected and one normal.

The other circumstance in which all twin pairs in an affected twin population would be concordant has already been alluded to; it is when the gene or genes determining a hereditary trait are universal in the population. In these two circumstances, the proportions of identical and fraternal twins will be the same in the concordant group as they are in the general twin population.

B. Postnatal, Nongenetic Influences.—If a disease or trait is dependent upon some environmental factor, operating after birth, one or both twins of a pair may be affected. Both CT and DT pairs should show the proportions characteristic of twins in the general population.

C. Genetic Traits Little Influenced by Environment.—Let us collect an affected twin series in which the trait being studied is hereditary and not influenced to any appreciable degree by environment. The twins are then separated into concordant and discordant groups. The proportion of IT and FT will differ in the two groups. In the CT there will be a concentration of identical, and therefore, of like-sexed twins, while in the DT only FT will be found, in which like- and unlike-sexed twins will be equal.

The proportions of CT found in the affected twin population that are either identical, or are of like sex, will differ widely dependent upon two conditions: (1) the mode of inheritance exhibited by the trait studied, and (2) the frequency of the gene or genes determining the trait. The proportions of identical, also of like-sexed twins among CT rises from those found in the general twin population (one-third and two-thirds, respectively) to one as the mode of inheritance of the trait shifts from dominant to recessive, to two or more factors; and as the frequency of the gene or genes causing the trait falls from one toward zero (Table III).

TABLE III

	1. PER CENT OF CT THAT ARE IDENTICAL	2. PER CENT OF CT THAT ARE OF LIKE SEX	3. PER CENT OF DT THAT ARE OF LIKE SEX
Universal heredity or prenatal environment	33.3	66.7	no DT
Rare dominant trait	50.0	75.0	50.0
Rare recessive trait	66.7	83.3	50.0
Rare trait dependent upon 2 equally occurring rare recessive genes	89.0	94.4	50.0
Mutation	100.0	100.0	50.0

The proportion of IT chosen as representative of the population proportion is $\frac{1}{3}$. The values assigned to the percentages of twins under each trait are the limiting values which will be realized as the trait becomes so rare that the proportion of genes causing it approaches zero. As each trait becomes progressively more common in the population, the values in each of the three columns approach those characteristic of universal heredity.

Ratios in Twins Affected With Genetic Traits Having Small Probability of Occurring in Two Sibs.—If there is little likelihood that the trait will affect two children in a family, one will find practically no FT among the CT, hence the latter will be made up almost entirely of twins of like sex; and practically all of these will be IT. Conversely, when among the CT of an affected twin population the proportion of like-sexed twins significantly exceeds the two-thirds

value found in the general twin population, the trait in question is probably inherited in a manner sufficiently complex that the probabilities of two sibs being affected are practically nil.

The affected twin method should not be used for traits which are common in the population. For these, other easier methods of studying the inheritance are available. If, however, the trait is rare or seldom affects more than one child in the family, the twin method may be the only one which gives a hint of the solution. If the human geneticist knows only the sex of the twins, some of the value of the data is lost; if he has an accurate statement from the obstetrician reporting the case that the twins are identical or fraternal, including the criteria upon which the judgment of their identity is made, the data become more valuable. It is too lengthy a process to show by what means the formulas for analysis of traits by the twin methods were derived; they will be reported elsewhere. Suffice it to show here some indication of the line of argument, and to emphasize when a disease or abnormality exists in one or both of the twins that it is essential for future genetic analysis that the sex, zygosity (whether identical or fraternal), and the presence of the trait in one or both twins be accurately and adequately reported.

Frequently, the trait studied is sufficiently rare so that no one man sees enough of it in twins to make a study from his own cases. He must rely on the published cases for his analysis. It is the purpose of this article to urge the adequate and accurate recording of diseases in twins by the medical profession so that the medical geneticist may use the records.

This problem has been stated on the basis of what would be found if certain conditions were fulfilled. In practice, of course, the reverse is true; the results are obtained and the conditions which must have existed to give those results are arrived at by deduction. The manner in which twins can be used may be illustrated by the data on mongolism in twins.

TABLE IV. TWINS WITH MONGOLOID IMBECILITY

	BOTH AFFECTED	ONE AFFECTED	TOTAL
<i>A. Zygosity Known.—</i>			
Identical twins	10 pairs	1 pair	11
Fraternal twins, like sex	3 pairs	12 pairs	15
Fraternal twins, unlike sex	0 pairs	24 pairs	24
	13 pairs	37 pairs	50
<i>B. Sex Known.—</i>			
Like-sexed twins	17 pairs	22 pairs (9MM,13FF)	
Unlike-sexed twins	0 pairs	24 pairs (MF)	

The two totals do not agree, since some twins were reported without the statement being made as to their being identical or fraternal.

It is evident that mongolism cannot be determined (either solely, or largely) by prenatal conditions because 74 per cent of the twin pairs show discordance, in place of 0 per cent. It is probably not caused by a single gene; from evidence in single cases of mongolism we are certain that it is neither dominant nor recessive, and the evidence from twins confirms this. The percentage of concordant twins that are identical is 77, a value lying between 66.7 and 89 (Table III). The percentage of CT that are of like sex is 100, a value which is attained when a mutation is involved and approached when even two or more genes are involved.

One might consider that mongolism is a trait which is not always expressed when the causative environment operates, thus explaining the frequency of DT in this group. The sex ratio of the DT pairs, however, is practically one-half

like-sex to one-half unlike-sex (22:24) characteristic of FT. This ratio is the expected one if mongolism has a genetic basis with complete penetrance, so that all DT will be of the FT type. Although no definite conclusion can be drawn, it would seem that mongolism is determined by a complex of genetic factors, completely penetrant, and such that the probabilities for two sibs being affected are approximating those found when a trait is dependent upon two rare recessive genes or upon some other combination of multiple genes.

Summary

Distortions of population proportions of IT and FT, and of sex ratios in a series of twin pairs may be used to determine whether traits are genetically determined, and in the case of rare dominant or recessive traits, the mode of inheritance as well. This applies only to series of twin pairs collected because one twin at least shows the trait in question.

A hereditary trait universally present in the population from which the twins come, or a trait determined exclusively by nongenetic intrauterine factors should occur always in both members of a twin pair, if present at all. Such twin pairs will exhibit sex ratios characteristic of twin pairs in the general population.

A trait which is conditioned exclusively by postnatal environmental factors, may occur either in one or in both twins of an affected twin population. In both the CT and DT groups, there will be an approximation to the population twin ratios.

Twin pairs exhibiting a congenital trait, practically exclusively genetic in origin, will show a distortion of sex ratios in twin pairs of both the CT and DT groups. The CT will have a concentration of like-sexed twins beyond the value found in an usual twin sample. DT will show a close approximation to the $\frac{1}{2} : \frac{1}{2}$ ratio of like to unlike sex characteristic of FT. The degree of departure from the values found in the general twin populations may give an indication, especially in rare traits, of the mode of inheritance of the trait in question.

If a trait is genetic in origin but also modified by environmental factors, some of the IT will be found in the DT. The greater the role of the environment, the more discordance will be found among IT.

Physicians are urged to publish all cases of disease or abnormality in twins, for future genetic analysis. The following information is essential for such analysis: (1) Sex of both twins. (2) If one only is affected, sex of normal twin, as well as of affected twin. (3) If twins are of the same sex, state whether they are identical or fraternal and give criteria upon which such judgment is based, blood groups, including A, B, O; M, N; and Rh groups if possible; hair, eye coloring, weight, height, ease with which they can be distinguished, palm and fingerprints, and any other items in which they may differ from the general population. Do not submit as evidence of identity or lack of it, the conditions of membranes and placentas, unless the twins were in the same sac, with no partition between, or if a partition is present, give report of a microscopic examination, if the twins are of the same sex. Such a body of data will ultimately allow the medical geneticist to find answers to some questions unsolved at present.

Reference

1. Pickering, G. H.: *Brit. M. J.* 2: 988, 1946.

VAGINAL HYSTERECTOMY AND COLPECTOMY FOR PROLAPSE OF THE UTERUS AND BLADDER

JOHN T. WILLIAMS, M.D., F.A.C.S., BOSTON, MASS.

(From the Whidden Memorial Hospital)

THE purpose of this article is to call attention to an operative procedure which the writer has worked out over a period of several years which has proved very effective in properly selected cases of prolapse of the uterus and bladder.

Crossen¹ has truly said concerning operations for prolapse: "The objectives vary somewhat in different cases and the methods for attaining the objectives are different for different conditions. No one operation is best for all varieties of cases." The operation to be described is reserved for elderly women in whom preservation of the vaginal tube is not essential. The principles of the operation are: first, complete extirpation of the vaginal walls, second, vaginal hysterectomy, and third, the sewing together of the pubococcygeus muscles in the median line, thus giving excellent support to the bladder and rectum.

Martin² was the first to suggest colpectomy with vaginal hysterectomy for prolapse, but he failed to make use of the pubococcygeus muscles which is the most important step in the operation.

Of the innumerable operations which have been devised since the days of Emmet, Hegar, and Lawson Tait, those in use today may be grouped under five classifications. These are:

1. The Manchester-Fothergill operation.
2. The Watkins interposition operation.
3. Vaginal hysterectomy with anterior and posterior colporrhaphy (Mayo and others).
4. Colpocleisis (the Le Fort type operation).
5. Vaginal repair and fixation of the uterus.

The techniques of these various operations are too well known to require description here. The Fothergill operation probably is based on the soundest anatomical principles. It is nevertheless not an easy operation to perform well and many operations so-called are done which are not really Fothergill operations. The interposition operation is very satisfactory in a limited group of patients, namely, those who have passed the menopause but in whom atrophy of the uterus has not yet taken place.

The Mayo type of operation, vaginal hysterectomy with suture of the cardinal ligaments beneath the bladder, is open to the criticism that frequently the cardinal ligaments are too stretched out and weak to give adequate support to the bladder. The various types of colpocleisis, Le Fort and others, should be reserved for very elderly patients in poor condition.

The old operation of vaginal repair and uterine fixation is still useful where the function of childbearing has to be preserved, but the condition is sufficiently severe to cause invalidism unless some operation is done. In these cases it is the writer's procedure, after extensive repair of the anterior and posterior vaginal walls, to open the abdomen and suture the uterus to the undersurface

of the anterior sheath of the rectus. This is done by four catgut sutures passed through the fascia and the anterior surface of the uterus, the upper one being placed near the fundus. If the uterus is drawn up as high as possible before placing the sutures, the end results have been quite satisfactory. In the event of subsequent pregnancy, delivery must be done by cesarean, but this has not proved too difficult.

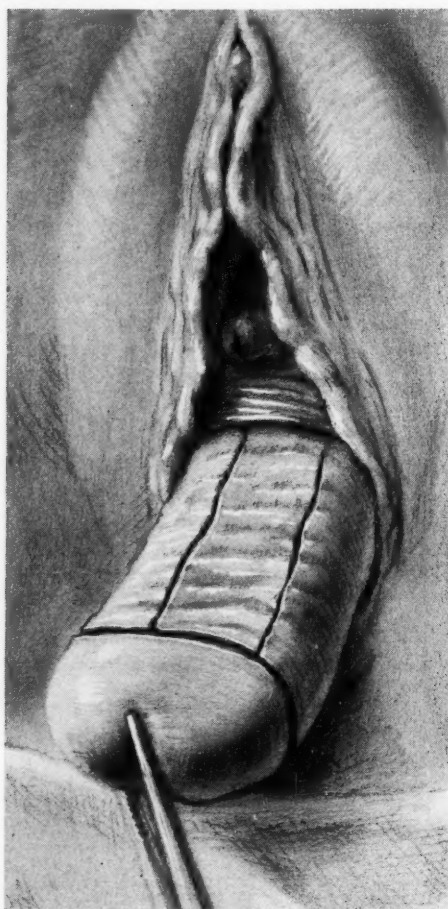


Fig. 1.

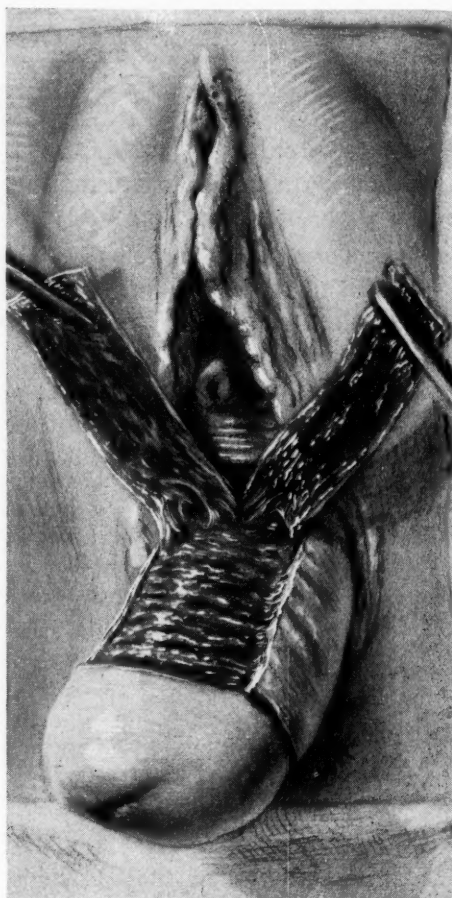


Fig. 2.

Fig. 1.—Vaginal flaps outlined before removal.

Fig. 2.—Separation of the anterior vaginal flaps. The posterior flaps to be freed subsequently.

The indications for and limitations of vaginal hysterectomy and colpectomy have already been stated. The fundamental part of the operation is the suture together of the pubococcygeus muscles throughout their entire length. According to Stander's description,³ the pubococcygeus consists of a band of muscle fibers 2 to 2.5 cm. in width which arises from the horizontal ramus of the pubis 3 to 4 cm. below its upper margin and 1 to 1.5 cm. from the symphysis. Its fibers pass backward and encircle the rectum and possibly give off a few fibers which pass behind the vagina and it is then inserted in the coccyx. These muscles can be easily felt in the unanesthetized patient about one inch inside the vaginal orifice and are easily picked up by the needle or Allis forceps after denudation

of the vaginal wall. These muscular bundles are quite substantial and when united give excellent support to the bladder and rectum.

Spinal anesthesia after mild premedication is preferred as most of these patients are elderly. I have done a few operations under local infiltration anesthesia.

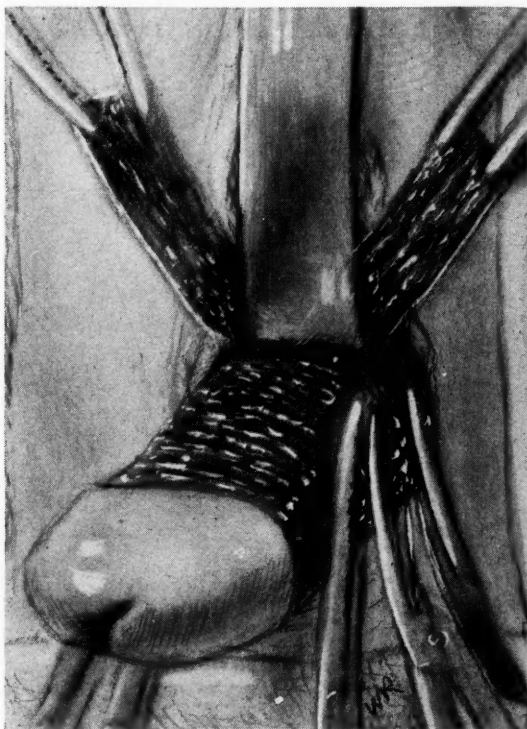


Fig. 3.—The bladder has been separated from the uterus and is held back by a retractor. The cardinal ligaments are being divided between clamps.

Technique of Operation

The patient is placed in the lithotomy position and is prepared aseptically, and the bladder is emptied by catheter. The cervix is seized with a tenaculum forceps and drawn downward. A circular incision is made at the junction of the cervix with the vaginal walls. Four longitudinal incisions are then made at right angles to this circular incision and carried to just within the vaginal orifice. All these incisions pass just through the vaginal wall, but no deeper. (Fig. 1.)

The four flaps thus marked out are separated from the structures beneath, that is, the uterus, bladder, and rectal wall, being started with scissors and then peeled off by blunt dissection. (Fig. 2.) The bladder is then separated from the uterus as in a vaginal hysterectomy. The peritoneum is then opened anteriorly and posteriorly exposing the cardinal (Mackenrodt's) ligaments and the broad ligaments with the proximal portion of the Fallopian tubes. A retractor is inserted to hold up the bladder and these structures are clamped and divided (Fig. 3) and the uterus removed.

The cardinal ligaments which contain the uterine artery and the broad ligaments containing the ovarian artery are doubly ligated. The vaginal flaps are then cut away close to the vagino-cutaneous junction (Fig. 4). In the illustrations only the instruments being actively used are shown.

The peritoneum is closed by a running suture. Then the stumps of the cardinal ligaments are sewed together after the method of Mayo beneath the bladder. (Fig. 5.)

The next step is the most important part of the operation. The pubococcygeus muscles are brought together in the median line by a series of interrupted catgut sutures (Fig. 6). This gives a firm support to the bladder and rectal wall and completes the obliteration of the space formerly occupied by the vagina. The cut edges of the vaginal walls are then united by interrupted sutures. (Fig. 7.) Coaptation sutures, as shown in Fig. 6, may be placed including the vaginal wall and muscle, but are not absolutely essential.

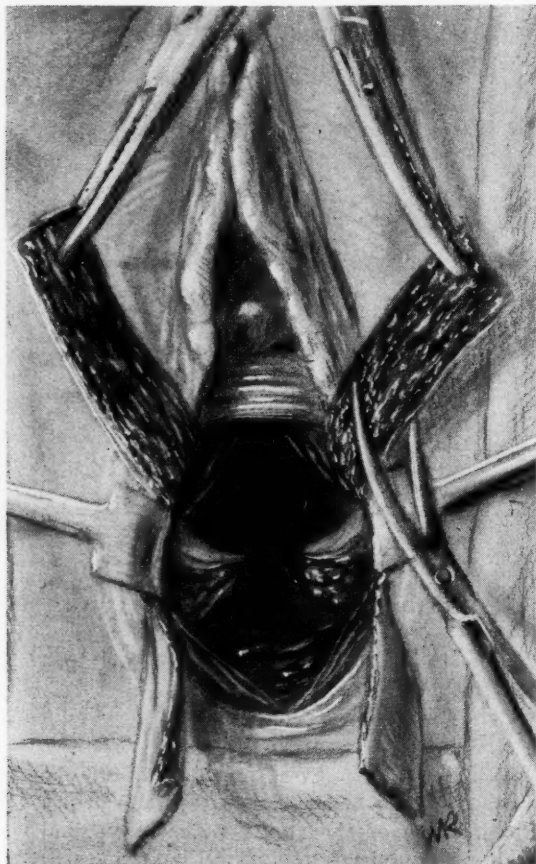


Fig. 4.

Fig. 4.—The uterus has been removed. The stumps of the broad ligaments are seen. The vaginal flaps are being cut away.

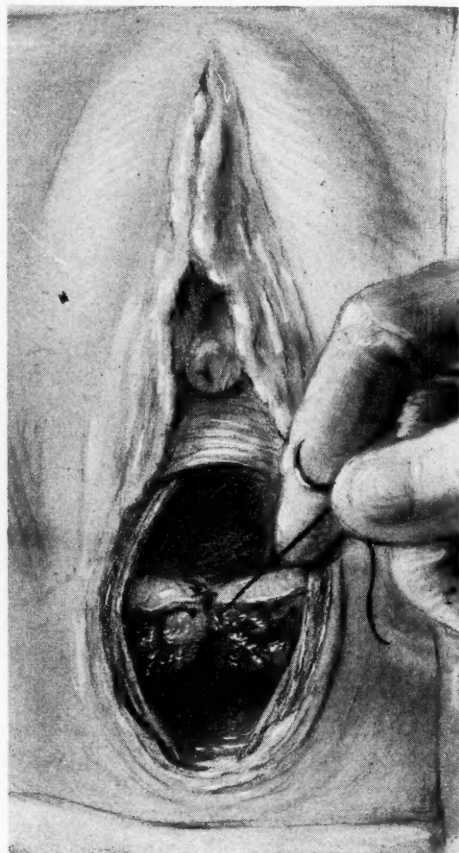


Fig. 5.

Fig. 5.—The stumps of the broad and cardinal ligaments, having been ligated, are being sewed together.

After the conclusion of the operation the vagina is replaced by a shallow cul-de-sac never over one inch in depth. There is no possibility of recurrence of cystocele or rectocele because of the firm floor formed by the united pubococcygeus muscles.

The operation is not difficult technically for any surgeon experienced in vaginal operating. There is seldom any shock and bleeding is usually controlled by the ligation of the cardinal and broad ligaments and a few small bleeding points in the denuded areas which are ligated individually.

The aftertreatment is simple. Constant drainage of the bladder by a Foley catheter is maintained for five to seven days. Diet is given as tolerated by the patients, adequate

fluids by mouth or intravenously being most important. A small suds or glycerine enema is given on the fourth day.

If the patient's condition will allow, she is kept in bed eight days to avoid undue strain on the sutures and to insure better healing. Penicillin 300,000 units daily should be given for five days.

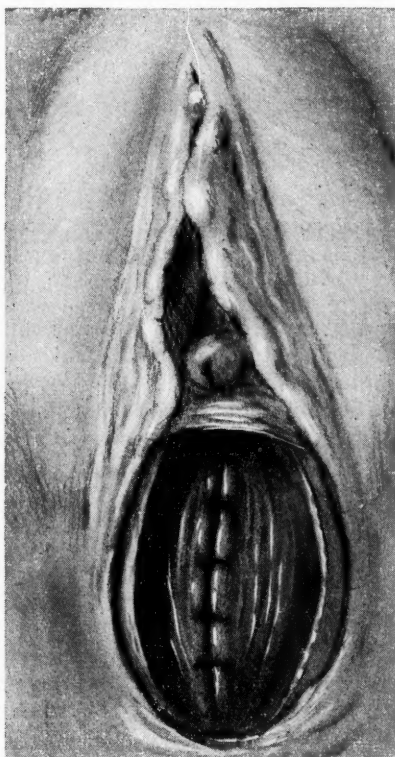


Fig. 6.

Fig. 6.—The pubococcygeus muscles have been sutured together through their entire length, closing completely the pelvic diaphragm. This is the most important step of the operation.

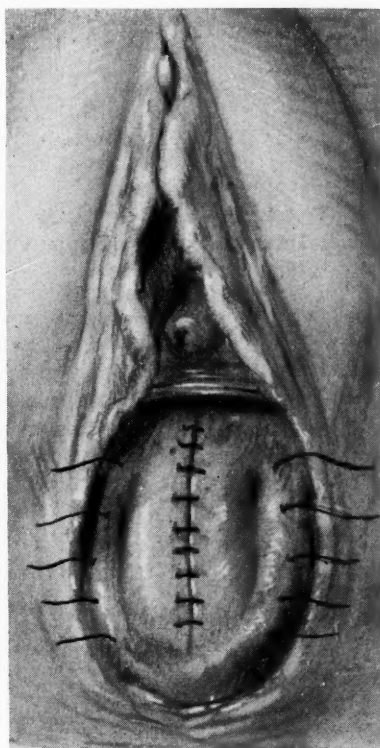


Fig. 7.

Fig. 7.—The cut edges of the vaginal walls have been brought together, completing the operation.

Results

I have performed this operation in about sixty cases of varying degrees of prolapse with satisfactory result in all but two. One had some incontinence of urine before operation which appeared to be worse following operation, and there was one death. The death was in a woman of 64 years of age, who had intestinal obstruction due to a loop of small intestine becoming adherent to the peritoneum at the site of the hysterectomy. An attempt to relieve the obstruction by a Miller-Abbot tube was unsuccessful and operation was performed as a last resort, but the patient's condition was too poor for survival.

Conclusions

Vaginal hysterectomy and colpectomy are satisfactory operations for prolapse of the uterus and bladder in elderly women.

The technique is not difficult for any surgeon experienced in vaginal operating.

References

1. Crossen, H. S., and Crossen, R. J.: *Operative Gynecology*, St. Louis, 1938, The C. V. Mosby Co., p. 422.
2. Martin, A.: *Ztschr. f. Geburtsh. u. Gynäk.* 82: 1-8, 1920.
3. Stander, H. J.: *Williams Obstetrics*, ed. 8, New York, 1941, D. Appleton-Century Company, pp. 351-352.

Marshall, Victor Fray, Marchetti, Andrew A., and Krantz, Kermit F.: The Correction of Stress Incontinence by Simple Vesicourethral Suspension, Surg., Gynec. & Obst. 89: 509, 1949.

The authors describe a simple operation consisting of elevation and immobilization of the vesicle neck and urethra by suturing them to the pubis and rectus muscles. They have found that this operation produces good results in stress incontinence, especially in cases tested previously which respond satisfactorily to temporary elevation of the vesicle neck. In 44 suitable cases excellent results were obtained in 82 per cent and significant improvement in 7 per cent; there was no improvement in 11 per cent. Poorer urinary control did not result in any instance.

L. M. HELLMAN.

Crawford, Joseph B., Collins, Conrad G., and Weed, John C.: The Cervical Stump. An Analysis of 123 Cases, Surg., Gynec. & Obst. 89: 465, 1949.

In the table below the authors cite the symptoms referable to diseased cervical stump. In 123 cases where conservative methods for treatment of various pathological conditions of the cervical stump had failed, the cervix was removed vaginally in 121 cases and transperitoneally in two. There was no mortality. One hundred nine of the patients were completely relieved of their symptoms. There was no relief in three.

TABLE I. SYMPTOMS

	NO. CASES	PER CENT
Pelvic pain	66	53.6
Leucorrhea	60	48.7
Bloody discharge	49	39.8
Dyspareunia	39	31.7
Backache	35	28.4
Urinary discomfort	40	32.5
Bearing down pain	21	17.1

L. M. HELLMAN.

FREQUENCY OF THE Rh ANAMNESTIC REACTION DURING PREGNANCY

CHARLES L. SCHNEIDER, PH.D., M.D., DETROIT, MICH.

(From the Woman's Hospital)

IN THE Rh anamnestic reaction of pregnancy the production of Rh antibody is not greatly different than in pregnancies with Rh incompatibility such as may lead to erythroblastosis.¹⁴

In fact, the antibody titers are so similar in the two reactions as not to be of value in determining which pregnancy carries an rh-negative fetus and which an Rh-positive fetus.¹⁴

Thus, this anamnestic reaction of pregnancy is not only of theoretical interest but becomes clinically significant because of the problem of its differential diagnosis and of its frequency.

In the study below, the frequency of the Rh anamnestic reaction for the D factor is estimated on a probability basis and also on the basis of cases observed in different series.

Results and Discussion

So far as is known, the anamnestic reaction can occur only if the mother has been previously sensitized. However there are no available data to determine whether every sensitized mother who carries an rh-negative fetus will actually develop an anamnestic reaction. Nevertheless, for the purposes of the present estimation it will be assumed that she would do so. It will be further assumed that the d/d conceptus is not susceptible to any form of erythroblastosis fetalis and has essentially no other genetic handicap associated with his Rh status. The calculated incidence of the anamnestic reaction would be, then, the frequency with which an already sensitized mother would be expected to carry a d/d fetus, i.e., an rh-negative fetus.

For present purposes an increasing anti-D titer in any pregnancy in which the mother and baby are both d/d will be considered as an anamnestic reaction. Similarly, the occurrence of an increasing anti-D titer in any pregnancy of a d/d mother carrying a D/d fetus will be considered as an incompatibility reaction regardless of whether the result is clinical or subclinical erythroblastosis.

To base the calculation on the D factor alone is comparable to the bulk of the available data on erythroblastosis since the typing serum heretofore available has been generally of this specificity. Furthermore the D incompatibilities include 90 to 95 per cent of the cases of erythroblastosis.^{5, 10} Correspondingly, the D factor is believed to be the most strongly antigenic of the Rh-Hr antigens, although not to the exclusion of the other Rh-Hr factors.² Since a preliminary sensitization is essential and since type D seems to be by far the most likely to provide sensitization, the anamnestic reactions would also be expected to be preponderantly of D specificity. The specificity of Rh anamnestic reactions has been determined thus far only in the accompanying report¹⁴; it was concluded to be of type D in each of the three cases studied.

Similar calculations for anamnestic reactions could be applied to each of the five remaining Rh-Hr antigens if sufficient data were available. In view of the rarity of sensitization to these factors, however, the results probably would not significantly alter the over-all incidence of Rh anamnestic reactions.

Similar ABO anamnestic reactions, whether frequent or infrequent in pregnancy, likewise may be of little significance in differential diagnosis since the A and B antibodies rarely lead to erythroblastosis.¹⁶

Ratio of Anamnestic to Incompatible Reactions

This would be essentially the ratio of benign to pathologic Rh reactions.

1. *Calculated Ratio.*—

On a probability basis, the expected percentage of pregnancies of adequate prior sensitization and having an Rh status suitable for an anamnestic reaction was tabulated and is plotted in Fig. 1.

For this calculation it was assumed that on the average, two previous incompatible pregnancies would be necessary for adequate sensitization. The percentage incidence of D/D and D/d husbands was taken into account; for Caucasians with a 15 per cent incidence of d/d these percentages are 37.2 and 47.6 as calculated from the binomial theorem.^{6, 10} The curve of Fig. 1 indicates that the over-all ratio of conditions suitable for an anamnestic reaction as compared with the incompatibility reaction approaches a limit as the number of pregnancies increases, i.e., with increasing parity. The number of pregnancies necessary to reach this limit, but *not the limit itself*, is affected by the number of incompatible pregnancies assumed to be necessary for adequate sensitization. The limit is approached earlier if calculated for each pregnancy rather than on a cumulative basis (Fig. 1).

The results shown in Fig. 1 are calculated on the assumption of monogamous mating, and the limit calculated for the anamnestic reaction is approximately 28 per cent of the total reactions of pregnancy in which the antibody is produced.

The limit approached for random mating can be similarly derived. The calculated frequency of anamnestic reactions is then somewhat higher because some of the matings to d/d men can give rise to reactions, all of which would be anamnestic; these could have given no reactions at all under conditions of monogamous mating because of the absence of a mechanism for sensitization of the mother. The limit calculated with random mating is 39 per cent. A tendency toward the same limit might be anticipated in the presence of a considerable number of sensitizations by transfusion.

The over-all limit for the population as a whole must lie somewhere between these values—approximately 33 per cent. This gives an over-all upper limiting ratio of anamnestic to incompatible reactions of 1:2, as listed in Table III. It will be seen below that the observed ratio is somewhat less.

Without intentional selection of cases, a scarcity of anamnestic reactions and, conversely, a preponderance of incompatible reactions appear during the first few pregnancies, Fig. 1. This depends largely on sensitization at an earlier pregnancy among matings with D/D husbands; in these matings, since every baby would be Rh positive, there would be an incompatible Rh reaction at an earlier pregnancy, as early as the second or third, perhaps rarely the first: there would be no possibility of an anamnestic reaction at any parity. By contrast, on the average, women mated to heterozygous D/d husbands would require twice as many pregnancies for sufficient sensitization to be eligible for an anamnestic reaction, on the average perhaps four or five. In present hospital series there are relatively few mothers of this parity; hence the anamnestic reactions could be expected to be relatively infrequent. Stated in a positive manner, present hospital series might be expected to be heavily weighted with

the families of the "dangerous" D/D husbands.¹⁰ How rare rh-negative children are in actual series, and by inference, how preponderant the proportion of "dangerous" D/D fathers among them, is indicated in the obstetric and pediatric series below.

2. Ratio of Normal to Erythroblastotic Children With One or More Erythroblastotic Siblings.—

Three series^{1, 11, 19} of mothers chosen on this basis are available. The data are presented in modified form in Figs. 2 to 4; abortions are not included in the percentage calculations because evidence is lacking that they are caused by Rh incompatibility.^{1, 10} However, these may cause sensitization^{1, 10}; hence for comparison, abortions and stillbirths are plotted below the abscissa.

It is to be seen from Figs. 2 to 4 that with the first few pregnancies, the percentage of children with erythroblastosis increased rapidly with increasing parity, yet seemed not to increase beyond a limit in which approximately one-half to two-thirds of all births were of erythroblastotic children. It is tempting to suggest that the normal children may have been for the most part rh negative. However, such was not the case for as can be readily seen in Table I, among those children who were available for typing, only a small percentage were rh negative; this was true for all three series (Figs. 2, 3, and 4) and for such other data as can be collected (Table I).

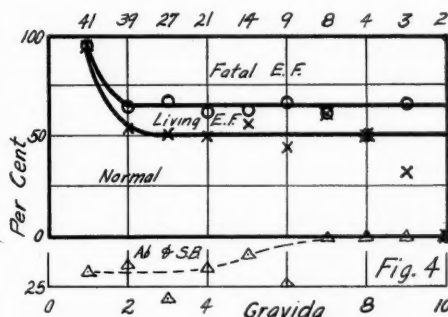
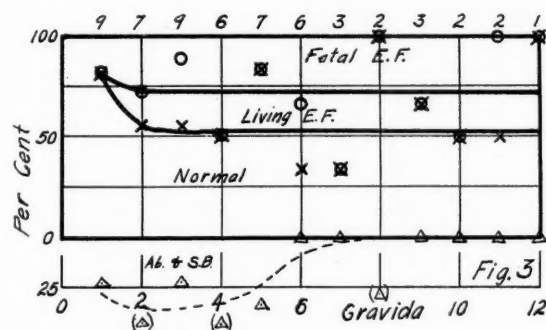
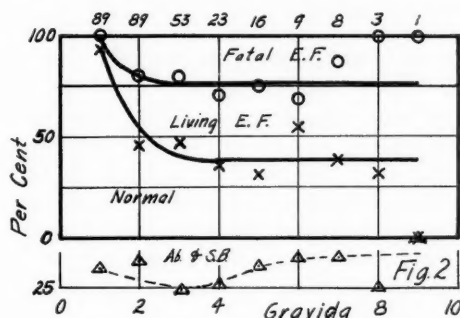
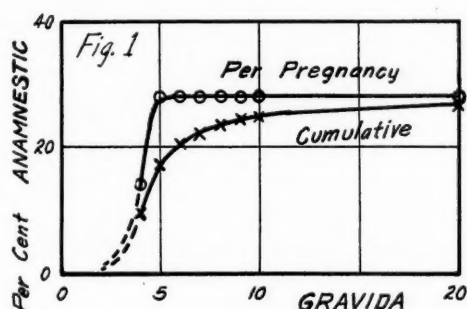


Fig. 1.—Proportion of anamnestic D reactions, at increasing numbers of pregnancies (increasing gravida), as percentage of the total pregnancies having an increase of D antibody.

Fig. 2.—Percentages of normal and of affected children from successive pregnancies of mothers having at least one erythroblastotic child. Numbers at top of graph are numbers of pregnancies of that parity. From data of Zuelzer.¹⁹

Fig. 3.—Same. From data of Chown.¹

Fig. 4.—Same. From data of Race and associates.¹¹

If the matings of these mothers had been on a truly random basis as to D/D or D/d husbands, it could be calculated on the basis of the distribution

of these two types and the frequency of their D and d gametes, that of the offspring 28 per cent (Fig. 1) or 28.7 per cent (Potter¹⁰) should have been rh negative, considerably higher than the values as calculated from different sources, shown in Table I. Only Philpott, Latour, and van Dorsser⁹ can state on the basis of a small but special series that their rh-negative children "... incidentally, represent the number of good children predictable"; their proportion being 25 per cent (Table I).

TABLE I. PERCENTAGE OF rh NEGATIVE (d/d) CHILDREN IN FAMILIES WITH ONE OR MORE ERYTHROBLASTOTIC CHILDREN

SOURCE	NUMBER OF CHILDREN TYPED		PER CENT rh NEGATIVE
	TOTAL D/d + d/d	d/d	
Predicted (above) if husbands are D/D or D/d by random distribution			29
Race, Taylor, Cappell and McFarlane, ¹¹ 1943	26	1*	4
Philpott, Latour, and van Dorsser, ⁹ 1946	8	2	25
Potter, ¹⁰ 1947	102	4	4
Chown, ¹ 1948	33	4	12
Zuelzer, ^{18, 19} 1948	58	7	12
Total	227	18	7.9

*This one case can now be classified as a probable rh negative, although not so classifiable at the time of the investigation (see text).

It is clear that the paucity of rh-negative children in these series is more in agreement with a preponderant selection of families of matings to D/D fathers, than with random selection. This has been pointed out previously by Race and co-workers,¹¹ who calculated the expected incidence of subsequent rh-negative children in their series on the assumption of an unintentional selection of cases, and find their data to be not widely discordant with this assumption. They calculated that 3.25 babies of a total of 26 under consideration in their series should have been rh negative. Although their series indicated no rh-negative children at the time of the report, it can now be entertained in the light of subsequent discovery of Rh-Hr types in addition to D, and from their description of the peculiar agglutinating behavior of the erythrocytes of the last child of their family No. 15, that at least this one child (Table I, above) of their series was probably rh negative in the same sense as its mother. This increases the tendency of their data to agreement with their explanation that families of homozygously positive D/D men were preferentially selected by the very nature of the study. The theoretical incidence of rh-negative children that they could calculate for their series, 13 per cent, is of the order of magnitude of the values in Table I.

In summary, the occurrence of normal children among families having erythroblastotic children is approximately in agreement with the theoretical number of children predicted to be not susceptible to the antibody by virtue of being rh negative, yet the agreement is superficial only, the actual incidence of rh negative children in these families being small. These data imply that in the series there is an unintentional and marked selection of families of matings to D/D men.

In the series next below the frequency of anamnestic reactions is estimated from observational data of titers rather than by calculation or by inference from incidence of rh types without measurement of antibody titers.

3. Anamnestic to Incompatible Ratio Determined by Titers Among Obstetrical Series.—

The available data, summarized in Table II, indicate that the observed proportion may be as much as one-half of the calculated maximum.

TABLE II. RATIO OF D ANAMNESTIC AND OF D INCOMPATIBLE REACTIONS IN OBSTETRICAL SERIES

INVESTIGATORS	NUMBER OF PREGNANCIES		RATIO	PER CENT ANAMNESTIC
	ANAMNESTIC	INCOM-PATIBLE		
Calculated (above)			1:2	33
Observed				
Page, Hunt and Lucia, ⁸ 1946				
Duration of antibodies in weeks ante-				
partum 1-9	1	7	1:7	13
10-14	2	8	1:4	20
15-36	2	10	1:5	17
Kozlow ^{4, 14} (Woman's Hospital, Jan., 1947- July, 1948)				
Erythroblastosis and/or rising antibody titer:	3	16	1:5	16
Total	8	41	1:5	16

Incidence of Anamnestic Reactions

1. *Calculated.*—This is shown in Table III for a population of high incidence of d/d (Caucasian) and for a population of low incidence of d/d (Oriental).

TABLE III. ESTIMATIONS OF INCIDENCE OF RH ANAMNESTIC REACTIONS OF PREGNANCY IN TWO DIFFERENT POPULATIONS*

	RACIAL GROUP	
	CAUCASIAN	ORIENTAL
Incidence of d/d, per cent	15	1.5 ^{13, 17}
Incidence of d/d conceptus among markedly sensitized mothers, assuming:		
Random mating	39	12
Monogamous mating	26	11
Therefore, approximate over-all ratio, anamnestic to incompatible reactions to D	1:2	1:8
Therefore, estimated incidence of anamnestic reaction among the entire population	1:800	1:32,000

*With the exception of the final calculations, which are based on an incidence of erythroblastosis among Caucasian births⁹ of 1:404, these calculations are for upper limits. The calculation of the incidence among Orientals is by proportion with the incidence of rh genotypes among Caucasians, making use of the known tenfold difference of d/d in the two populations, and by using the fourfold difference of the ratio of anamnestic to incompatible reactions listed in the table.

Infrequent as is the estimated incidence, 1:800 for an Rh₀ or D anamnestic reaction among Occidentals, yet a considerably smaller incidence of the D anamnestic reaction for Orientals is indicated in Table II, of the order of 1:32,000 pregnancies; the actual incidence may be less. This makes it unlikely that D anamnestic cases would be discovered at all in a survey in the Orient unless they were sought by study of selected families.

Conversely, of those few cases of erythroblastosis fetalis or of an anamnestic reaction occurring in the Orient, there may be a relatively greater proportion due to Rh-Hr factors other than D.

Because of the changing vogue of typing and cross-matching for transfusions there may be observed a relative and actual increase of both hemolytic and anamnestic reactions to Rh-Hr factors other than D among Caucasians in the not too distant future. Just as many of the cases of erythroblastosis now encountered are traceable in all or in part to sensitization by previous transfusion of D incompatible blood, so in the future, other Rh-Hr reactions of pregnancy may be traceable to sensitization due to the ever-increasing frequency of trans-

fusions compatible for D but without regard to the other Rh antigens. If observations in male patients who have received multiple transfusions is a guide, such a trend toward these other sensitizations is already well under way.²

2. Observed Incidence Among Obstetrical Series.—

The incidence of anamnestic reactions among Caucasians can be calculated from some obstetrical series thus far published. Two large series^{3, 12} do not list this status at all. Calculation from the series with available data are listed in Table IV.

TABLE IV. INCIDENCE OF RH ANAMNESTIC REACTION AS CALCULATED FROM DATA OF DIFFERENT OBSTETRICAL SERIES

CALCULATED FROM DATA OF:	NUMBER OF PREGNANCIES			INCIDENCE OF PREGNANCIES	
	TOTAL	INCOM-PATIBLE	ANAMNES-TIC	INCOM-PATIBLE	ANAMNES-TIC
Calculated incidence (above)					1:800
By extrapolation from special series (by Rh typing, titers not available): Philpott, Latour, and van Dorsser, ⁹ 1946	12,112			1:404	1:1200
By antibody titers: Page, Hunt, and Lucia, ⁸ 1946	"Over 4,000"	25	5	1:160	1:800
By erythroblastosis and/or antibody titers: Kozlow ⁴ , ¹⁴ Jan., 1947-July, 1948*	6,185	16	3	1:390	1:2000

*This series includes only the clinic portion of the hospital series and such cases as were referred to the laboratory by their private doctors for Rh testing. Hence it is possible that only a portion of the Rh-negative mothers were detected and that of these not all had antibody titers run. Therefore, a number of anamnestic cases may have been overlooked; by comparison with the series of Page and co-workers (next above in the table) it would appear that approximately one-half of the incompatible reactions also escaped attention.

The importance of the anamnestic reaction centers about the individual case. Even high antibody titers are not helpful in determining whether the fetus in the given case is Rh positive or rh negative.¹⁴ However, if the father's type were known to be D/D, it would follow genetically that the baby would always be D/d and some degree of erythroblastosis might be anticipated. If the father were known to be D/d there would be a fifty per cent chance of an anamnestic reaction or of an incompatible reaction. To determine the heterozygous D/d status with certainty requires anti-d serum, which at present is not available for clinical tests. However, presumptive genotyping⁷ of the Rh status has been performed ever since the introduction of the method by Taylor and Race.¹⁵ At present the D/D or D/d status can be determined on a presumptive basis, with known degrees of certainty for different Rh factor combinations, by testing with anti-c (and, when available, with anti-e) in addition to anti-C, -D, and -E. Hence the probability of an rh-negative baby and therefore of a benign anamnestic reaction, with a resultant normal baby, in a given highly sensitized mother, could be presumptively indicated in some cases without anti-d serum. In such cases with a presumptive D/d father, the chances of a d/d baby would be almost 1:1—information of considerable advantage over the general probability of 1:6 found above.

Summary

1. The scarcity of reports of the Rh anamnestic reaction during pregnancy suggests that this reaction may not be common.
2. The limiting frequency of Rh anamnestic reactions during pregnancy was estimated. This was done by estimating the frequency of rh-negative

babies among rh-negative mothers who would have been expected to have become sensitized to the Rh factor.

3. According to this calculation, the proportion of anamnestic reactions should approach, as its upper limit, one-third of all Rh reactions of pregnancy, among Caucasians.

4. Because Rh antibody reactions occur at earlier parity in matings to the "dangerous" homozygous fathers, and because the reactions of these matings can be incompatibility reactions only, and since actual obstetrical series necessarily include many small families, the expected proportion of anamnestic reactions in actual practice is less than 1:3. The proportion that can be deduced from recorded series is approximately 1:6.

5. The calculated incidence among all pregnancies for the Rh anamnestic reaction is approximately 1:800. The actual incidence which can be deduced from the few obstetric and pediatric series thus far published tends to be of this order of frequency or less.

6. In practice, one benign anamnestic reaction out of every six Rh reactions of pregnancy is sufficient to justify efforts at differential diagnosis. In the individual case a diagnosis of a heterozygous D/d father, a diagnosis which can be made only on a presumptive basis, but this with a known degree of certainty, would increase the likelihood of this benign reaction almost to 1:1.

7. Since the several prophylactic and therapeutic treatments for erythroblastosis remain to be of proved value, and since some of these, including early termination of pregnancy, are major procedures with inherent risks to mother or child, or both, they should be applied, if at all, only after the possibility that the reaction is a benign one has been excluded.

References

1. Chown, B.: Blood, Special Issue No. 2: 155, 1948.
2. Hattersley, P. G.: J. Lab. & Clin. Med. **32**: 423, 1947.
3. Kariher, D. H.: Virginia M. Monthly **73**: 347, 1946.
4. Kozlow, L. A.: In preparation.
5. Levine, P.: J. A. M. A. **128**: 946, 1945.
6. Levine, P.: Am. J. Clin. Path. **16**: 597, 1946.
7. Mollison, P. L., Mourant, A. E., and Race, R. R.: Medical Research Council Memorandum No. 1948, His Majesty's Stationery Office, London.
8. Page, E. W., Hunt, M., and Lucia, S. P.: Am. J. Obst. & Gynec. **52**: 794, 1946.
9. Philpott, N. W., Latour, J. P. A., and van Dorsser, G. J. E.: AM. J. OBST. & GYNEC. **52**: 926, 1946.
10. Potter, E. L.: Rh: Its Relation to Congenital Hemolytic Disease and to Intragroup Transfusion Reactions, Chicago, 1947, The Year Book Publishers, Inc.
11. Race, R. R., Taylor, G. L., Cappell, D. F., and McFarlane, M. N.: Brit. M. J. **2**: 289, 1943.
12. Sacks, M. S., Kuhns, W. J., and Jahn, E. F.: AM. J. OBST. & GYNEC. **54**: 400, 1947.
13. Schneider, C. L., and Hughes, C. H.: Igaku (Medicine), Kyoto **4**: 33, 1948.
14. Schneider, C. L., Beaver, D. C.: Kozlow, L. A., and Zuelzer, W. W.: AM. J. OBST. & GYNEC. In press.
15. Taylor, G. L., and Race, R. R.: Brit. M. J. **1**: 288, 1944.
16. Velez Orozco, A. C.: Blood, Special Issue No. 2: 164, 1948.
17. Wiener, A. S.: Am. J. Clin. Path. **16**: 477, 1946.
18. Zuelzer, W. W., Wheeler, W. E., and Leonard, M. F.: Pediatrics **1**: 799, 1948.
19. Zuelzer, W. W.: Personal communication.

PHEOCHROMOCYTOMA COMPLICATING PREGNANCY*

GEORGE L. BOWEN, M.D., DEAN J. GRANDIN, M.D., EDWARD E. JULIEN, M.D.,
AND SHEPARD KRECH, JR., M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, The Lenox Hill Hospital)

PHEOCHROMOCYTOMAS (paragangliomas, adrenal medullary tumors) have been of increasing interest in recent years. The first report of one causing hypertension was in 1899, another in 1914, and one in 1922. In these three cases the diagnosis was made post mortem. The first one diagnosed in life was in 1926. In 1927 Dr. Charles H. Mayo¹ reported a case of paroxysmal hypertension which was cured by the successful removal through the abdomen of a retroperitoneal nerve tumor located mesial to the left kidney. Since 1936 the medical literature has contained several reviews of the syndrome of "paroxysmal hypertension" due to these tumors. The occurrence in pregnancy of pheochromocytomas with their accompanying clinical syndrome is rare; in a search through the literature we have found only five case reports.²⁻⁶

The following case report with discussion is presented to point out the similarity between this syndrome and toxemia of pregnancy, and to stimulate interest in the clinical diagnostic measures for discovering these tumors.

The patient, I. M., a 26-year-old Puerto Rican primigravida at term, was admitted to the obstetric ward of Lenox Hill Hospital, June 4, 1948; she complained of severe headache and slight generalized edema.

The past history was irrelevant. Her mother died of hypertensive cardiovascular disease three months previously. The menarche was at 12 years of age, menstruation occurred at intervals varying from one to six months, and was of four days' duration.

The initial physical examination in the clinic at twenty-two weeks revealed no abnormalities. The weight was 130 pounds, blood pressure 98/48, pulse rate 84, respiratory rate 16, hemoglobin 12 Gm., blood type B, Rh positive, Wassermann negative, and urine negative for albumin and glucose.

The first two trimesters of pregnancy were uneventful except for occasional slight ankle edema and a blood pressure recording of 146/80 at the end of the second trimester. The third trimester was similarly uneventful until the final four weeks. During the latter period the patient complained of increasing headaches, frontal in origin with radiation to the occiput and increasing edema. The blood pressure ranged from 126/80 to 134/92, the urine remained negative for albumin. The total weight gain for the forty weeks was 18 pounds. Treatment consisted of a regimen of rest, diet, and sodium restriction.

Admission examination revealed slight periorbital edema, two plus pretibial edema, blood pressure 150/100, pulse rate 76, and respirations 20. The ocular fundi revealed some arteriovenous spasm. The remainder of the examination was normal, the uterus was term size, and the vertex was engaged.

Laboratory studies revealed a normal blood count and a trace of albumin in the urine; blood chemistry: urea nitrogen 12.0, uric acid 3.6, carbon dioxide combining power 42.4, serum protein 5.4, serum albumin 4.1, serum globulin 1.3.

*Presented at a meeting of the New York Obstetrical Society, March 15, 1949.

Treatment consisted of bed rest, sodium restriction, sedation, and intramuscular magnesium sulfate. Ten hours after admission the blood pressure was 132/80, and the edema had decreased somewhat. Spontaneous rupture of the membranes occurred at this time, and four hours later labor started after the administration of castor oil and an enema.

The first stage progressed with effective uterine contractions. The blood pressure fluctuated between 140/90 and 170/110, remaining mainly around 150/100 and urinalyses revealed one plus albumin. For sedation Demerol and scopolamine were given at the second and eighth hours of the first stage. Intramuscular magnesium sulfate was given at the fifth hour and intravenous magnesium sulfate and hypertonic glucose at the eleventh hour to control the spikes in blood pressure. The final three hours of the first stage were marked by slow progress and a fetal heartbeat of 200 per minute.

After fourteen and one-half hours the cervix was fully dilated and the vertex descended to the pelvic floor. In view of the pre-eclampsia-like picture and the rapid fetal heart rate the second stage was terminated early by an easy low-forceps delivery under gas, oxygen, and ether anesthesia. A 4,100 gram infant resulted. A fetal heartbeat was present at birth but the baby never breathed. Postmortem examination showed some peritoneal hemorrhage, primary atelectasis, and some aspiration of amniotic fluid in the lungs. A skull examination was not done.

The placenta was expressed after a twenty-minute third stage with only a moderate blood loss, following which intravenous Ergotrate was administered. Immediately following the third stage the patient's blood pressure was 210/120 and the skin and mucous membranes were moderately cyanosed.

Morphine sulfate, intravenous magnesium sulfate, and hypertonic glucose and oxygen inhalations were administered. Five minutes later the blood pressure dropped precipitously to 110/60, the pulse rate was 140, the respirations 24, and the temperature 102° F. During the next ten hours the blood pressure alternated with sharp spikes and dips from 170/120 to 110/80, the pulse rate increased to 200, the respirations to 40, and the temperature to 106° F. The patient appeared throughout to be severely shocked with pale, cold skin, cyanotic mucous membranes and depressed sensorium. There was no evidence of uterine rupture and no abnormal vaginal bleeding.

Laboratory examinations at this time revealed red blood cells 3,850,000, hemoglobin 12.4 Gm., a trace of albumin in the urine, urea nitrogen 20.5, uric acid 5.3, glucose 194, carbon dioxide combining power 35.5, serum protein 6.6 Gm., hematocrit 43.8 per cent and the electrocardiogram showed auricular tachycardia. Treatment consisted of sedation, oxygen, penicillin, intravenous 10 per cent glucose solution and calcium chloride intravenously; the latter was given to rule out magnesium sulfate toxicity.

Ten hours post partum the blood pressure and pulse rate were not obtainable, the respirations were 40, the heart rate was 200 with a gallop rhythm and pulmonary râles appeared. Aminophylline and morphine were administered and rapid digitalization was begun. After another six hours there was some improvement with decreasing râles and a stronger slower heart rate. Suddenly while the patient was being "prepared" for the night, acute left ventricular failure occurred. Tourniquets were applied to the extremities, aminophylline and glucose were administered intravenously without response and the patient expired.

The postmortem findings were as follows:

The heart was normal in size and shape with normal myocardium. The lungs showed marked chronic passive congestion. The liver showed central atrophy of the liver lobules, mild; and chronic passive congestion. The gastrointestinal tract was negative. The uterus was intact, the myometrium unremarkable, the tubes and ovaries were negative. The kidneys showed marked granular degeneration of the convoluted tubules and some collecting tubules with karyolysis, swelling and desquamation of the tubular lining. This was considered postmortem degeneration. The glomeruli were almost entirely anemic. The arteries were normal, the venules were severely engorged.

The right adrenal was normal in size, shape, and position. The left adrenal was replaced by a cystic mass which weighed 100 grams, was round, and measured 5 cm. in

diameter. This tumor bulged from its retroperitoneal position into the abdominal cavity. Three small arteries and a single vein were identified. The surface, stripped of peritoneum, was smooth and dark red brown in color. In one area yellow cortical tissue was stretched over the surface. The tumor was not connected with the kidney and was easily shelled out of its areolar bed. On section, the tumor proved to be a cystic structure containing in its single cavity thick red-brown turbid fluid. The wall varied in thickness from 2 to 20 millimeters. The tissue forming the wall was soft, dull, friable, and of the same deep red-brown color. There was no distinct inner membrane. The inner surface was ragged but nonloculated.

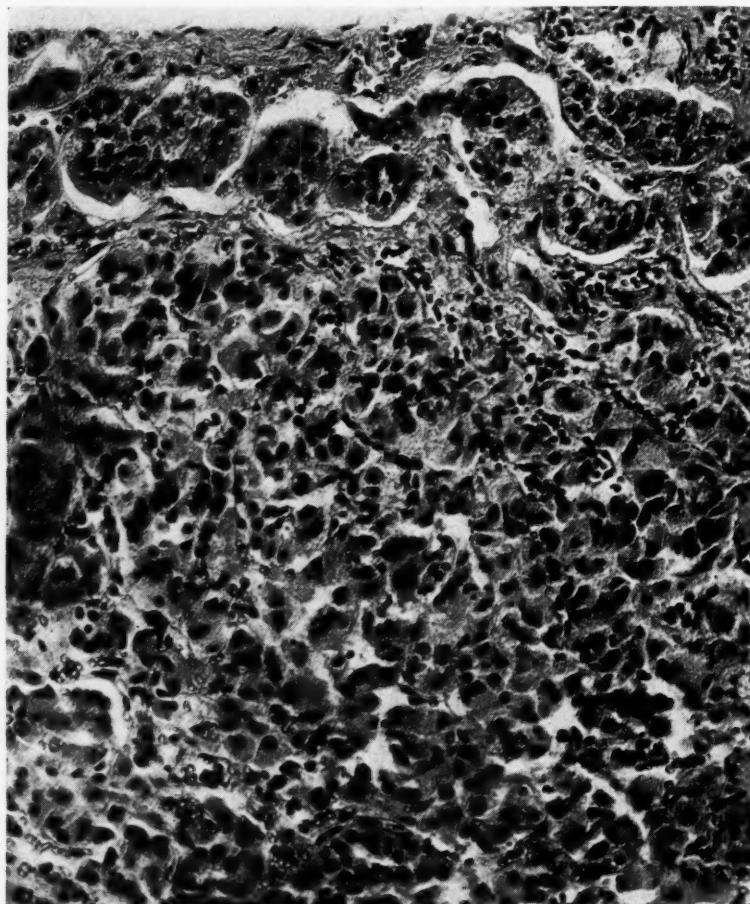


Fig. 1.—Left adrenal tumor showing compressed cortex and area beneath it.

The microscopic examination of the left adrenal gland showed the capsule was markedly widened by fibrous tissue (Figs. 1 and 2). The cortex was atrophied, markedly narrowed, and the three zones were not distinct. The cortex formed part of the border of a large tumor mass which occupied the medulla and lay within the widened capsule.

The tumor consisted of rounded polygonal or elongated cells, which were loosely arranged in nests and sheets incompletely separated by delicate fibrous stroma. The orderly arrangement was generally more marked beneath the capsule. As the central cavity was approached, the tissue was disrupted. There was no distinct lining to the cavity. Where best differentiated the nuclei were round or ovoid, generally pale, vesicular, and frequently they showed a prominent nucleolus. The cytoplasm was homogeneously compact

and finely granular and showed increased eosinophilia. In some tumor areas small hemorrhages were seen. Occasional giant cells were present. There was a marked degree of necrosis with disruption of the sheets and cords of tumor cells.

The diagnosis was pheochromocytoma of the adrenal gland accompanied by evidence in the lungs and liver of heart failure.

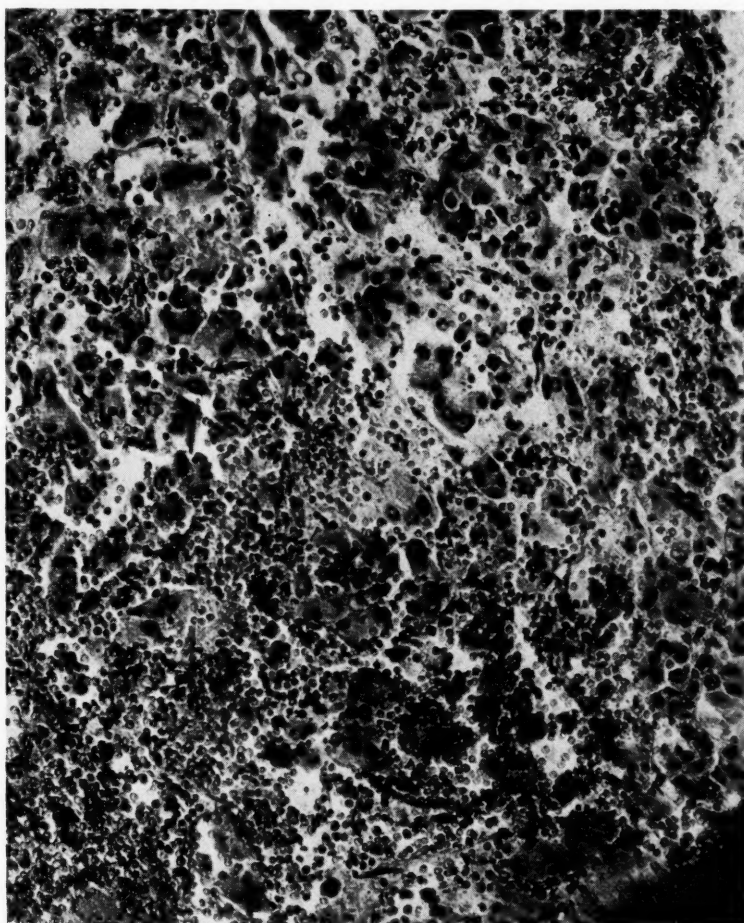


Fig. 2.—Showing medullary portion of tumor approaching the cyst cavity.

Biological assay* of the tumor fluid was determined by kymographic recordings of the blood pressure using a 2.8 kilogram cat. When a 1 to 100,000 solution of Adrenalin was injected intravenously, using 0.1 c.c. per kilogram, a rise in the blood pressure resulted. Then the same quantity of the tumor fluid (0.1 c.c. per kilogram) was injected into the cat and this caused a rise of blood pressure approximately threefold over the elevation resulting from the Adrenalin. Dilutions of the tumor fluid were then used and a dilution of 1 to 100 resulted in a rise in blood pressure similar to that obtained from 0.1 c.c. of 1 to 100,000 Adrenalin. From this information it was estimated that the tumor fluid contained 1 mg. of epinephrine per cubic centimeter.

Following the above experiment benzodioxane (5.0 mg. per kilogram) was given intravenously. This prevented a rise in blood pressure when the adrenalin and tumor fluid were again administered.

*Biological assay was done through the courtesy of Merck & Co., Inc.

The benzodioxane used was the one described by Fournau and Bovet⁷ as 933 F (piperidylmethyl benzodioxane). They found this substance to have an "adrenolytic" action when used in strengths of 0.25 to 2 mg. per kilogram.

Comment

The clinical syndrome associated with a pheochromocytoma is of interest in obstetrics because it includes symptoms of pre-eclampsia and eclampsia. Also because of the severe shock one must consider rupture of the uterus and hemorrhage. The clinical impression in this case was that of an atypical severe pre-eclampsia.

The symptomatology is the result of the liberation of epinephrine from the tumor. Beer, King, and Prinzmetal⁸ in 1937 first demonstrated high amounts of epinephrine in the blood during a hypertensive crisis.

The clinical picture may be characterized by several or all of the following: headache, epigastric pain, palpitation, dyspnea, tachycardia, rarely bradycardia, sweating, increased respiratory rate, nausea and vomiting, elevation in blood pressure varying hourly or daily, pale cold skin, glycosuria, and azotemia. Cardiac failure may ensue and a state of shock, possibly fatal, may follow an attack. Occasionally malignant hypertensive disease may be simulated. Smithwick⁹ in his series of 1,000 hypertensive patients who were treated by lumbo-dorsal sympathectomy, found pheochromocytoma at the adrenal site in 0.5 per cent of them. It has been estimated that 15 per cent of pheochromocytomas may be extra adrenal.

Freeman, Freedman, and Miller¹⁰ in 1941 showed that the shock produced in dogs by the prolonged administration (one to one and one-half hours) of intravenous Adrenalin (0.0034 to 0.0164 mg./kg./min.) was caused by vasoconstriction of peripheral vessels causing anoxia of the peripheral tissues, increasing the capillary permeability with a loss of plasma from the blood stream into the tissues.

These tumors are found more frequently in women between the ages of 20 and 40 years, the childbearing era. The attacks may be initiated by varying degrees of manipulation, or activity such as palpation, bending, injections, operations, anesthesia, and sometimes emotional crises.

The diagnosis may be made by clinical findings, roentgenograms including pyelograms and perirenal insufflation techniques.

In the past three years five pharmacological diagnostic tests have been described:

- (1) Histamine, 0.03 mg. intravenously¹¹;
- (2) Mecholyl, 25.0 mg. subcutaneously¹²;
- (3) Tetra-ethyl-ammonium bromide, 3 c.c. intravenously¹³;
- (4) Epinephrine insensitivity, 1:1,000 epinephrine subcutaneously¹⁴;
- (5) Benzodioxane intravenously.^{7, 9}

The first three cause a rise in the blood pressure with pheochromocytoma, whereas in normal individuals there is usually a drop in blood pressure.

The epinephrine insensitivity test is dependent upon the fact that a patient with pheochromocytoma will tolerate large amounts without a resulting hypertension.

The benzodioxane test would seem to be most helpful in the differential diagnosis of unusual hypertension in pregnancy. Benzodioxanes are adrenolytic substances and cause marked lowering of the blood pressure only in syndromes due to pheochromocytomas. Normal individuals and hypertensive patients may react with a mild pressor response.

The differential diagnosis has usually been between cerebral tumors, other causes of convulsions, hyperthyroidism, diabetes, and malignant hypertension

when the blood pressure is persistent. In pregnancy this tumor causes symptoms of a severe pre-eclampsia or eclampsia, and the severe shock causes one to consider uterine rupture and hemorrhage.

The treatment consists of surgical removal of the tumor. Careful pre-operative and postoperative care is necessary. Cahill¹⁵ emphasized the importance of ligating all tumor vessels before handling the tumor at operation. The administration of epinephrine may be necessary postoperatively to offset the sudden drop in blood pressure.

This patient had severe attacks of paroxysmal hypertension with resultant shock. The cardiac failure is consistent with the fluctuating hypertension and shocklike state. It is of interest that the final episode of cardiac failure occurred as the patient seemed to be improving, and following manipulation and movement of the patient in preparation for the night, which probably resulted in massage of the tumor thus liberating more epinephrine and precipitating the fatal attack.

Summary

1. A case of pheochromocytoma complicating pregnancy is presented. Only five case reports of this condition associated with pregnancy have been found in the literature.
2. The similarity of this syndrome to toxemia of pregnancy is noted.
3. Pharmacological aids for differential diagnosis are reviewed.

Bibliography

1. Mayo, Charles H.: *J. A. M. A.* **89**: 1047-1050, 1927.
2. Oberling, C., and Jung, G.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**: 366-371, 1927.
3. Burgess, A. M., Waterman, G. W., and Cutts, F. B.: *Arch. Int. Med.* **58**: 433-447, 1936.
4. Kelly, H. M., Piper, M. C., Wilder, R. M., and Walters, Waltman: *Proc. Staff Meet., Mayo Clin.* **11**: 65-70, 1936.
5. Palmer, R. S., and Castleman, B.: *New England J. Med.* **219**: 793-796, 1938.
6. Bartels, Elmer C., and Kingley, J. A., Jr.: *Lahey Clin. Bull.* **6**: 7-12, 1948.
7. Fournneau, E., and Bovet, D.: *Arch. internat. de pharmacodyn. et de thérap.* **46**: 178, 1933.
8. Beer, Edwin, King, F. H., and Prinzmetal, M.: *Ann. Surg.* **106**: 85-91, 1937.
9. Goldenberg, Marcel, Synder, C. Harrison, and Aranow, Henry: *J. A. M. A.* **135**: 971-976, 1947.
10. Freeman, N. E., Freedman, H., and Miller, C. C.: *Am. J. Physiol.* **131**: 545, 1941.
11. Roth, G. M., and Kvale, W. F.: *Am. J. M. Sc.* **210**: 653-660, 1945.
12. Guarneri, Victor, and Evans, J. A.: *Am. J. Med.* **4**: 806-813, 1948.
13. LaDue, John S., Murison, Paul J., and Pack, George T.: *Ann. Int. Med.* **29**: 914-921, 1948.
14. Maycock, R. L., and Rose, E.: *Am. J. M. Sc.* **213**: 324-330, 1947.
15. Cahill, George F.: *J. A. M. A.* **138**: 180-186, 1948.

THE UTERINE CERVIX DURING PREGNANCY*

EDWARD J. MURPHY, M.D., AND PETER A. HERBUT, M.D., PHILADELPHIA, PA.

*(From the Departments of Gynecology and Obstetrics and of Pathology,
Jefferson Medical College)*

THE uterine cervix, during pregnancy, undergoes definite physiologic changes (Stieve,¹ Hofbauer,² Levey,³ and Fluhmann⁴). The most striking alteration occurs in the endocervical mucosa and glands. In the former, it consists essentially of a proliferation of the endocervical epithelium. It is manifested by numerous areas of active cell multiplication, and stratification of the tall columnar cells, with occasional downgrowth into the underlying stroma. These projections, however, as demonstrated with hematoxylin-molybdenum staining, are surrounded by an intact basement membrane. The cervical glands show increased activity as pregnancy progresses, with much mucin production, accompanied by branching and infolding of the epithelium into the lumina of the glands. The racemose glandular arrangement becomes more marked, occasionally assuming a corkscrew appearance, not unlike that seen in the endometrial glands. New glandular formations are seen as nests of large, deep-staining cells. The cervical stroma becomes markedly vascular and edematous, with increase in size and number of the individual cells.

These investigators record little or no change in the stratified squamous epithelium covering the cervical portio, and only an occasional occurrence of decidual formation in the stroma. Fluhmann,⁴ however, noted one well-developed decidual reaction, and isolated islands of decidua in eleven other specimens, in a group of thirty-two cases of cervical erosion during pregnancy.

The following study, consisting of a series of biopsies of the cervix during pregnancy, was undertaken to investigate further the cervical portio. Particular attention was paid to the possible occurrence of precancerous changes in the squamous epithelium and to the frequency of decidual formation.

Material

Biopsies were taken from the cervices of fifty pregnant patients, distributed evenly between primigravidas and multigravidas, with a gestation range from one and one-half to eight lunar months. Specimens were secured both from cervices that were grossly healthy and from those that revealed obvious erosions. Twelve of the patients were white; the remainder were Negro, and the ages varied between 17 and 41 years. All patients attended the maternity outpatient department of the Jefferson Hospital.

An ethmoid snare was utilized to secure the specimens after the cervix was painted with Zephiran solution. No tenaculum was employed to grasp the cervix, unless absolutely necessary, because of the tendency to bleed from the area upon removing the instrument. It was found that the bite of the snare

*Presented before the Obstetrical Society of Philadelphia, Nov. 4, 1948.

prevented the cervix from slipping away. One specimen was taken from each cervix, usually from the squamocolumnar junction, and from no constant quadrant of the portio.

As might be anticipated with the increased vascularity of the pregnant cervix, moderate bleeding was encountered in most instances. This was, however, readily controlled by pressure over the area with a cotton sponge. The average time for cessation of bleeding was three minutes. None of the cervixes bled longer than five minutes; there were no instances of recurrent bleeding, and none of the patients aborted, entered premature labor, or developed an antepartum infection.

The average removed specimen measured 12 by 8 by 6 mm. All were immediately fixed in formol-alcohol and subsequently stained by the hematoxylin-eosin method.

Results

As is seen in Table I, it is possible to classify the types of tissue alteration observed, into several categories:

TABLE I

TYPES OF TISSUE ALTERATION	25 PRIMIPARAS		25 MULTIGRAVIDAS	
	NUMBER	PER CENT	NUMBER	PER CENT
Alterations of endocervical tissue	22	88	23	92
Inflammatory changes	15	60	17	68
Inflammation at the squamocolumnar junction	6	24	15	60
Increased basal-cell activity	2	8	1	4
Increased thickness of squamous mucosa	25	100	25	100
Epidermization	5	20	4	16
Decidua formation	5	20	6	24
Edema and increased vascularity	25	100	25	100

A. Alteration of the Endocervical Mucosa and Glands.—

This consisted essentially of the well-established and often-observed changes outlined earlier in this article. All of the tissues presented these modifications to a greater or lesser degree, except in five instances, where no endocervical or glandular mucosa was incorporated in the specimens.

B. Inflammatory Changes.—

1. Moderate to diffuse infiltration with inflammatory cells was noted in sixty-four per cent of all cases. As seen in Table II, this compares closely with the percentage of inflammatory reaction in Fluhmann's⁴ series.

TABLE II

TYPES OF TISSUE ALTERATION	PRESENT SERIES, 50		FLUHMAN'S SERIES, 32	
	NUMBER	PER CENT	NUMBER	PER CENT
Alterations of endocervical tissue	45	90	24	75
Inflammatory changes	32	64	21	65.6
Increased basal-layer activity	3	6	4	12.5
Epidermization	9	18	6	18.7
Decidual formation	11	22	11	34.3

2. Inflammation at the squamocolumnar junction (Fig. 1). This was an extremely interesting finding, and was noted in twenty-one, or 42 per cent, of all cases, and in 65.6 per cent of those showing inflammatory changes. This predilection was observed in 24 per cent of the primigravidas and in 60 per cent of the multigravidas. It consisted essentially of an infiltration of plasma cells,

neutrophils, and histiocytes, concentrated in the submucosal stroma, with a gradual diminution in number, on moving away from the squamocolumnar junction. Increased cellular activity, as evidenced by epidermization, decidual formation, and stratification of the basal-layer cells, seemed to coincide with increased inflammatory-cell concentration. Conversely, the cervixes showing a minimal amount of inflammation manifested a sparseness of cellular activity.

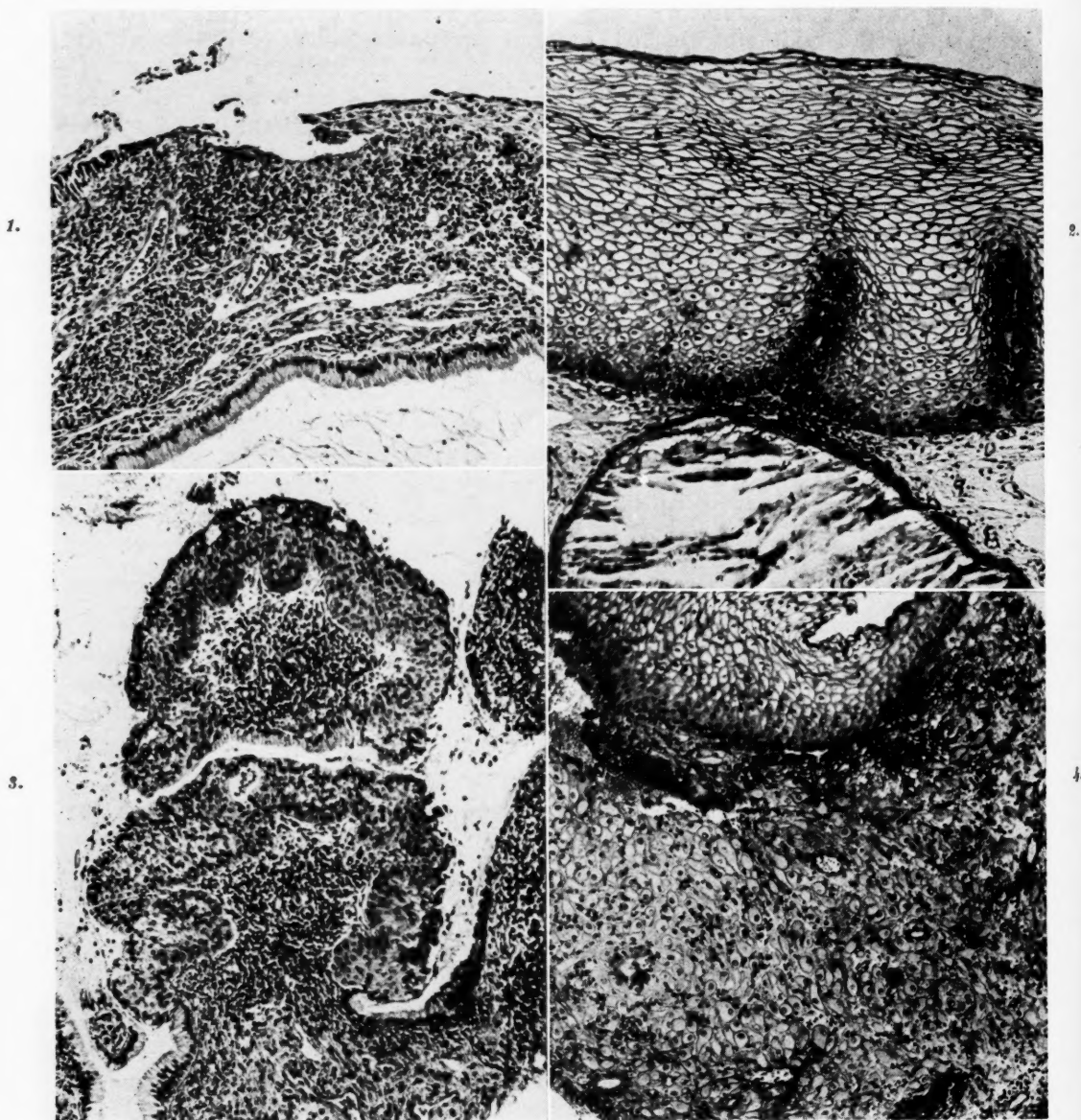


Fig. 1.—Marked inflammation at the squamocolumnar junction.

Fig. 2.—Thickening of stratified squamous epithelium, with clearing of the individual cells.

Fig. 3.—Process of epidermization.

Fig. 4.—Marked decidual reaction.

C. *Alterations of the Squamous Epithelium.*—

1. Increased activity of basal layer. This was found in three instances, or 6 per cent of all cases. Despite the greater staining affinity of the individual cells, and an increased thickness of the basal layer, there was no evidence of stromal invasion. The division into basal layer, prickle-cell layer, superficial vesicular and parakeratotic layers was not abolished, and the cells retained their regularity of size and shape, with a minimum amount of mitotic activity.

2. Increased thickness of the outer layers. All specimens showed an increase in thickness of the stratified squamous epithelium, effected by multiplication of cells in the superficial zone. The individual cells revealed a marked clearing of the cytoplasm, due most likely to glycogen deposition, with a tendency to, but not true pyknosis of, the nuclei (Fig. 2). The modification of the superficial cellular layer can be easily understood on the basis of this layer's ready response to hormonal stimulation.⁵

D. *Epidermization.*—

This process, designated by some pathologists as metaplasia, was encountered in nine instances, or 18 per cent. As illustrated (Fig. 3), the underlying stroma, in most instances, contained a marked infiltration of inflammatory cells. The columnar epithelium had been replaced by the undermining proliferating basal layer of the squamous epithelium, with differentiation of the latter into layers. In other specimens the epidermization followed the glandular trestles as is often seen in the nonpregnant cervix.

E. *Decidual Formation.*—

Marked to patchy decidual-cell formation was found in the stroma of specimens from eleven patients, or 22 per cent. In every instance, this occurred as a polyp or polypoid projection of the endocervical mucosa and was associated with peridecidual inflammatory-cell infiltration. The decidual reaction was often so pronounced that it closely approximated the well-formed decidua of the endometrial stroma (Fig. 4).

F. *Edema and Increased Vascularity of the Stroma.*—

This was found in all specimens.

Discussion

The fundamental physiologic basis for the tissue alterations observed in this study is the markedly increased and sustained levels of estrogen and progesterone, elaborated early in pregnancy by the corpus luteum and later by the trophoblastic cells of the placenta. These levels have been estimated as increasing from 40 to 500 M.U. estrogenic substance per 100 c.c. of serum and from 10 to 60 mg. urine pregnandiol as pregnancy progresses.⁶ This effect is further enhanced by the increased vascularity and congestion incident to the enlarging uterus.

Under the impetus of this combination of physiologic synergists, the tissues of the Müllerian system attain a high level of cellular activity. In the cervix, this enhancement raises the important question of its possible role in the pathogenesis of carcinoma, the predilection of which for this structure is all too well known.

None of the tissues surveyed in this study showed either obvious or borderline malignant activity, nor were there any instances of intraepithelial carcinoma. As has been mentioned previously, both the hyperactive basal layers of the stratified squamous epithelium, and the stromal projections of the endocervical mucosa, were well within the confines of the basement membranes. The instances of epidermization, although often giving a bizarre appearance on a cursory investigation, on more careful scrutiny revealed no cause for alarm. Meyer⁷ states that transitions from benign epidermization to carcinoma are unknown.

In considering the occurrence of inflammatory-cell localization at the squamocolumnar junction, several interesting points present themselves. Ayre,⁸ in his recent article, premises the following three predisposing factors in the pathogenesis of cervical carcinoma: persistent estrogenic tissue concentration, thiamine deficiency, and chronic infection. Brunelli⁹ demonstrated that estrogens present in rabbit's blood will become fixed in inflamed tissues. Ayre,⁸ by utilization of the cytology of the cervical smears, with confirmation by biopsy material, concluded that the estrogenic tissue concentration increased as the squamocolumnar junction was approached. One may speculate whether the increased estrogenic effect is on the basis of increased concentration of the hormone at that site, or is due to a normal estrogenic concentration, the activity of which is augmented in some fashion by the inflammatory reaction in the immediate vicinity. To substantiate the latter premise, it is well known that the true estrogenic index of the vaginal smear is often difficult to evaluate in the presence of inflammation, as has been pointed out by Papanicolaou and Traut,¹⁰ Rakoff,⁵ and others.

In the present series, prominent inflammatory-cell concentration at the squamocolumnar junction was found in 24 per cent of the primigravid and 60 per cent of the multigravid patients. This marked disparity of occurrence in the two groups becomes significant when one considers that cervical carcinoma occurs approximately sixteen times more frequently in multiparous women.¹¹

If Ayre's⁸ postulation of chronic inflammation as a predisposing factor in carcinogenesis is correct, the eradication of infection should reduce the incidence of carcinoma of the cervix. Cashman,¹² employing deep cauterization of the cervix in a series of ten thousand cases, reports a decrease of 80 to 85 per cent in the occurrence of cervical carcinoma in his series of approximately four and one-half thousand follow-up examinations.

These observations would indicate that chronic inflammation is, if not carcinogenic *per se*, at least a prominent agent in complex genesis of cancer.

The role of chronic irritation in the enhancement of cellular activity is further emphasized by the finding of decidual formation in 22 per cent of the present series. Isolated instances of decidual formation in the pregnant cervix have been reported by Hennessy,¹³ Klein,¹⁴ von Zatzko,¹⁵ Levey,³ Hofbauer,² and many others. However, Fluhmann⁴ found an incidence of 34.3 per cent in his cases of cervical erosions.

The irritative factor functioning in the production of the decidual transformation of the stroma is evident on noting that every instance of its occurrence in the present series was observed in a polyp or or polypoid projection of the endocervical mucosa, and was invariably surrounded by chronic inflammatory cells.

Once again, one may speculate that the hormone content of the blood, in this instance progesterone or one of its metabolites, is fixed in this particular portion of the Müllerian system by biochemical forces, operating on an irritative basis, and perhaps enhanced in its effect on the stromal cells. A similar occurrence of events might be a factor in the finding of decidua in the tube or ovary, predisposing to ectopic gestation.

The higher incidence of decidual formation found by Fluhmann⁴ was perhaps due to the type of lesion biopsied. His cases all presented a cervical erosion, wherein irritative factors are more prominent.

These islands of decidual cells are physiologic counterparts of Loeb's¹⁶ experiments on the rabbit, wherein electrical stimulation of the uteri produced well-formed deciduomas, differing only in the type of irritating agent.

Whether the same combination of factors, namely, irritation and local con-

centration of estrogen, results in hyperactivity of the epithelial tissues and possibly malignant change, one may only hypothesize. Nevertheless, the similarity is sufficiently pronounced to suggest such a possibility.

Summary

1. A series of fifty biopsy specimens removed from pregnant cervixes is presented.

2. No instance of frank carcinoma, or so-called intraepithelial carcinoma, was encountered.

3. The well-established alterations of the endocervical mucosa and glands were observed in all instances where these tissues were present in the removed specimen.

4. The squamous epithelium revealed thickening of the superficial layers, in all instances. However, hyperactivity of the basal-layer cells was present in only 6 per cent of the cases.

5. Epidermization was seen in approximately 20 per cent.

6. Inflammatory-cell infiltration occurred in 64 per cent of the biopsies. However, concentration of the reaction at the squamocolumnar junction was seen approximately three times more frequently in the multigravidas. The possible relationship of this predilection, in the pathogenesis of carcinoma, is discussed.

7. Decidual reaction was noted in 22 per cent. A hypothesis of the physiopathologic relationship of chronic irritation to hormonal tissue concentration is presented.

References

1. Stieve, H.: *Ztschr. f. mikr.-anat. Forsch.* 11: 291, 1927.
2. Hofbauer, J.: *AM. J. OBST. & GYNEC.* 25: 779-791, 1928.
3. Levey, H. B.: *AM. J. OBST. & GYNEC.* 28: 234-240, 1934.
4. Fluhmann, C. F.: *AM. J. OBST. & GYNEC.* 55: 133-150, 1948.
5. Rakoff, A. E.: *AM. J. OBST. & GYNEC.* 47: 467, 1944.
6. Cantarow, A., and Trumper, M.: *Clinical Biochemistry*, ed. 3, Philadelphia, 1945, W. B. Saunders Company.
7. Meyer, R.: *Surg., Gynec. & Obst.* 73: 14-20, 1941.
8. Ayre, J. E.: *AM. J. OBST. & GYNEC.* 54: 363-389, 1947.
9. Brunelli, B.: *Arch. internat. de pharmacodyn. et de therap.* 49: 214, 243, 262, 295, 1935.
10. Papanicolaou, G. N., and Traut, H. F.: *Diagnosis of Uterine Cancer by the Vaginal Smear*, New York, 1943, The Commonwealth Fund.
11. Scheffey, L. C., Thudium, W. J., and Farrell, D. M.: *AM. J. OBST. & GYNEC.* 43: 941-954, 1942.
12. Cashman, B. Z.: *AM. J. OBST. & GYNEC.* 41: 216-224, 1941, and 49: 190-196, 1945.
13. Hennessy, J. P.: *AM. J. OBST. & GYNEC.* 46: 570, 1943.
14. Klein, J., and Domeier, L. H.: *AM. J. OBST. & GYNEC.* 51: 423-426, 1946.
15. von Zatzko, A.: *Zentralbl. f. Gynäk.* 61: 201, 1937.
16. Loeb, F.: *Zentralbl. f. Physiol.* 5: 22, 1928-1933.

Discussion

DR. PETER A. HERBUT.—From a practical point of view, I believe there are two points that bear emphasis. The first concerns itself with the squamous epithelium. Dr. Murphy has shown that the squamous epithelium does undergo a change in pregnancy, but he has also shown that this change does not in any way approach anything that resembles a carcinoma or a carcinoma in situ. It follows, therefore, that if a pregnant woman has a lesion in the cervix and if this lesion appears carcinomatous, then it probably is carcinoma and that patient had better be treated for it. The second point is the reaction that occurs in the stroma. Dr. Murphy has shown that the decidua is seen in about one-fifth of the

cervices. When the pathologist sees that picture histologically he has no difficulty in dubbing that as decidua. On the other hand, when the inflammation is sometimes very marked, when the basement membrane that overlies this decidua is broken, when the overlying epithelial cells are frayed and intermingled with the adjacent decidual cells, and when the decidual cells are sometimes distorted by inflammatory reaction, the pathologist may find it extremely difficult to distinguish this lesion from a true carcinoma. It follows therefore that in order to evaluate properly any case the pathologist must have more information than merely the patient's name.

DR. F. SIDNEY DUNNE.—Dr. Murphy has shown that it may be difficult to interpret the changes seen in the cervix during pregnancy unless one is well versed in histologic interpretation of early malignancy. There is no reason to mistake a carcinoma, whether it be early or well advanced, for inflammatory changes due to pregnancy. This paper also brings out the fact that it is not harmful to do a biopsy while the patient is pregnant. There were no miscarriages in his group of patients who had a biopsy during the pregnancy. We all know that carcinoma of the cervix can occur during pregnancy and if the bleeding is presumed to be due to the pregnancy and the patient is not examined and a biopsy taken, the carcinoma will be missed, or at least be allowed to progress beyond the cervix, whereas, if a biopsy were taken during the pregnancy, the diagnosis would be made much earlier.

Read, Grantly Dick: Observations on a Series of Labors With Special Reference to Physiological Delivery, The Lancet, p. 721, April 30, 1949.

The now well-known writings of Dr. Read deny a physiologic basis for pain in childbirth. Fear of childbirth is a social artefact. It causes protective sympatheticotonia, leading to resistant tension in the circular muscle fibers of the lower uterine segment. This increased resistance to the expulsive forces produces excessive tension, interpreted as pain.

Physiological (painless) childbirth is achieved by (a) good physical and mental preparation, (b) removal of fear by antenatal teaching and (c) *personal* supervision by the obstetrician during labor. Small doses of barbiturates, or chloral and bromides, are sometimes used to induce a restful initiation into labor, and morphine or Pethidine is offered as the cervix approaches or reaches full dilatation. During delivery patients may take a self-administered anesthetic. The mother may touch the baby during its birth, and may fondle or suckle it soon thereafter. The perineum remains intact in 52 per cent of primiparas and in 65 per cent of multiparas. The third stage is entirely unassisted, and expulsion of the placenta is described as an "extremely pleasing sensation."

In 481 deliveries thus conducted, 239 mothers (50 per cent) had no sedative or analgesic whatever. A group of 124 women (26 per cent) took some pain-relieving medication. Seventy-eight per cent of the patients cooperated well, and needed no anesthetic during delivery.

The conduct of physiological labor results in lessened blood loss and a decreased incidence of operative deliveries. The psychic trauma of childbirth is removed, leading to increased willingness to nurse (98 per cent of this series) and an absence of aversion to future childbirth.

IRVING L. FRANK.

DIVERTICULUM OF THE PREGNANT UTERUS

ORVAN W. HESS, M.D., F.A.C.S., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)

TRUE diverticulum of the pregnant uterus is an exceedingly rare finding. Only a few have been described in the literature.^{1, 2, 5} However, the grave potentialities of such an anatomical defect are readily apparent. The possibility of rupture of such an area of thinned-out uterine wall during labor, as well as the further hazard of serious intraperitoneal hemorrhage from placental tissue imbedded within the sac, demands careful survey of the uterine fundus during pregnancy.

Diverticulum of the uterus must be differentiated from the more common bicornis or didelphis uterus and, indeed, as suggested by DeLee and Greenhill,³ and Stander,⁴ the diagnosis is frequently confused. Since these developmental abnormalities are the result of failure of normal fusion of the Müllerian ducts, the finding of the round ligament or Fallopian tube arising from the lateral margin of such a tumor mass should favor ready identity in most cases. In contrast, a sac contiguous with the myometrium and opening into the uterine cavity, and bearing no such anatomical relationship to the cornual structures, can properly be considered a diverticulum. It would be anticipated that such lesions would be more eccentrically attached to the fundus.

The mechanism by which diverticula are produced in the uterus is not yet clear. It may be speculated that their occurrence could be related to an innate defect in a localized area of myometrium or might develop on the basis of deficient myometrium following trauma of curettage or myomectomy. It is possible that such a weakened area could also be produced by excessive lysis and invasion of the myometrium by trophoblastic tissues. In contrast with other tubular structures whose relatively thin walls contain smooth muscle and in which diverticula are common, even major defects of the myometrium may remain unrecognized until distention occurs during the growth changes and increase of intrauterine pressure of pregnancy. Similarly, pseudodiverticula may result at the site of poorly healed wounds of cesarean section.

Schickele and Freund (1904), at operation for vaginal bleeding from suspected placenta previa, reported the findings of a pouch originating from the isthmus of the uterus and lying entirely superior to the attachments of the round ligaments. This sac, composed of myometrium, contained the entire products of gestation with the placenta occluding its communication with the cavity of the uterus which had undergone only slight enlargement. More recently, the presence of a sac arising from the uterus in the region of the left cornu and containing the products of early gestation has been recorded by

Hawkins. In this instance, the round ligament and Fallopian tube were noted to be attached to its lateral border thus making the diagnosis of diverticulum less definite.

Two cases of diverticulum of the uterus, which were substantiated at operation, have been observed on the obstetrical service of the New Haven Hospital. In Case 1 here reported, the anomalous sac was found to arise from the posterior wall and cross the mid-line of the uterus while in Case 2 the diverticulum was found on the anterolateral wall inferior to the normally placed round ligament.

Case Reports

CASE 1.—R. G., No. B17169, aged 29 years, white, housewife, gravida i, had been married two and one-half years. For approximately two years she had experienced backache and "pain in tubes" during menstruation. Menses were irregular and often "seven to ten days late." First seen on Feb. 15, 1941, her last menstrual period had occurred on Sept. 15, 1940, and the estimated date of confinement was June 22, 1941. During October, November, and December, she had had slight vaginal bleeding associated with backache. For this she had consulted a surgeon who informed her that the "uterus was tipped slightly" and attempts were made to replace it by manual manipulation. Examination on February 15 revealed the fundus palpable 2 to 3 cm. above the umbilicus, no tenderness was noted. The fetal heart was not heard. The cervix was small and conical, fullness was noted in the cul-de-sac. A diagnosis of pregnancy of five months' duration in a retroverted, possibly infantile uterus was made. The history of bleeding suggested that previous detachment of small areas of placenta had occurred. One month later she reported that she had noted fetal movements. The fetal heart was audible in the right lower quadrant. During the subsequent two months she complained of episodes of mild lower right quadrant pain which was unassociated with tenderness or local spasm. X-ray pelvimetry was obtained on June 17, 1941. The pelvis was symmetrical, dolichopellic. The transverse diameter or the mid-plane measured 8.9 cm. The vertex was lying approximately 2 cm. above the ischial spines. No evidence of placenta previa was detected.

She was admitted to the New Haven Hospital on June 29, 1941, with the complaint of intermittent episodes of uterine contractions and lower abdominal discomfort during the previous forty-eight hours. On admission her general condition was good. Temp. 98.6° F., pulse 98, respiration 21, blood pressure 118/78, red blood cells 3.8 million, hemoglobin, 11.8 Gm.; urine, negative. She complained of occasional contractions. On examination the fundus felt somewhat tense; no tenderness was elicited, the fetal heart was heard in the right lower quadrant, the vertex was lightly engaged and poorly flexed. Medical induction procedures were followed by little apparent effect. Examination on June 30 disclosed the vertex above the ischial spines; the cervix barely admitted the tip of the examining finger, and soft "spongy" tissue was felt about the vertex. Active hemorrhage followed the examination and in view of the suggestion of placenta previa and the nature of the cervix, cesarean section was elected. Under cyclopropane anesthesia the uterus was exposed through a 10 cm. mid-line suprapubic incision. The anterior wall was smooth and normal in contour. There was no evidence of torsion. An adequate flap of peritoneum was dissected free from the lower uterine segment and a longitudinal incision was made in the uterus. The membranes were perforated and the amniotic fluid removed by suction. A foot was grasped and with moderate traction the buttocks were brought into view. As the lower abdomen was being delivered a huge ventral hernia was observed. This was covered by a thin membrane on the surface of which there was considerable hemorrhage along with visible peristaltic waves. Moderate bleeding from the uterine cavity ensued which was not readily controlled by the usual oxytocics. Search in the region of the internal os revealed the presence of numerous large blood vessels, apparently venules, in an intimately adherent edge of placenta which on the surface had a corrugated appearance suggestive of hydropic degeneration. Further examination revealed the placenta to be intimately adherent to the posterior wall of the uterus and to extend deeply into a large diverticulum, approximately 10 to 12 cm. in depth, on the posterior wall. The

uterus was readily delivered through the abdominal incision, no adhesions being encountered. The placenta was separated with some difficulty from the ballooned-out area and it was noted that, although there was apparent thickening of the uterine wall along the margin of the sac, the wall of the diverticulum was markedly thin and at its periphery was approximately 2 to 3 mm. in thickness and associated with paper-thin dimpling. In view of the unusual size of the diverticulum, the thinness of its walls, areas on the internal surface grossly suggestive of degeneration, and the risk of possible subsequent infection and hemorrhage, a hysterectomy was done. Immediate repair of the large ventral hernia of the newborn was done by a surgical team. Additional findings of dextrocardia and hydrocephalus added to the poor prognosis for the infant.

The postoperative course was uneventful and the patient was discharged on the thirteenth postpartum day.

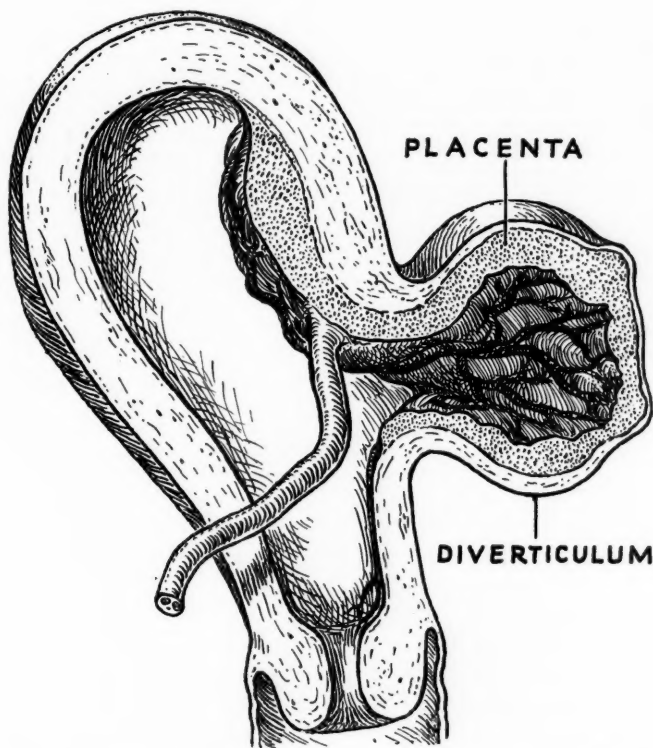
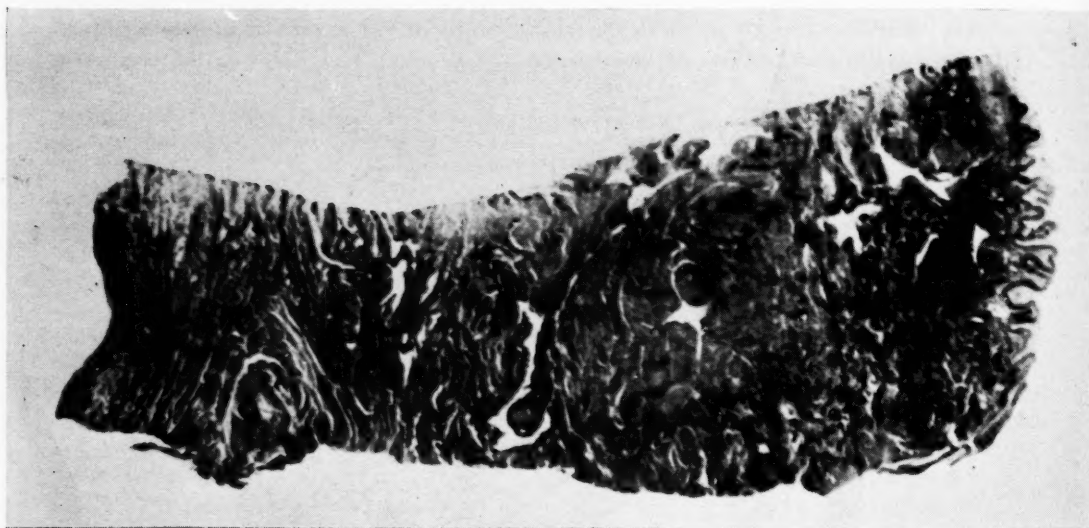


Fig. 1 (Case 1).—Diverticulum of posterior wall of uterus.

Pathological report: (G8606.) The specimen consisted of two parts: (1) The uterus was somewhat contracted, the wall measuring 2.5 cm. in thickness. There were some adherent membranes in the region of the left cornu which appeared faceted and in this region there was brownish discoloration. The membranes peeled away with some difficulty but the surface of the endometrium seemed smooth. There were no lumps or hard masses in it and no excessive hemorrhage. The serosa of the uterus was quite normal and there were no obvious fibroids. The wall of the uterus in the region of the implantation of the placenta on the posterior wall measured approximately 1 cm. in thickness instead of the average measurement of 2.5 cm. (2) The placenta measured 15 cm. in diameter with the cord attached eccentrically. There were several areas of thrombosis and several small calcific sacs. The cotyledons were all intact and of normal appearance.

Microscopic: A block (Fig. 2) was taken through the thinnest portion of the uterine wall. The external surface was covered with a layer of thin flat cells which were arranged regularly and in some spots covered with a layer of cuboidal epithelium and regularly dark-staining nuclei. Beneath this layer were some regularly arranged bundles of smooth muscle interspersed with quite large blood vessels. There was no inflammatory change or fibrosis.



A.



B.

Fig. 2 (Case 1).—Microscopic section of wall of diverticulum (B) contrasted with adjacent normal wall (A) of uterus. Note minimal infiltration of myometrium with decidua. ($\times 5$.)

In the lower muscle layer was found a regularly arranged layer of decidual tissue. The cells were arranged in cords and the blood vessels normal in appearance. There was evidence of minimal invasion of the decidual columns into the muscle, but no proliferation or anaplasia.

Diagnosis: Full-term pregnant uterus and normal placenta with thinning of myometrium in region of placenta.

CASE 2.—E. M., No. C2374, aged 35 years, white, Hungarian press-operator, had been married seven years. Past history was irrelevant except for apparent sterility during seven years of marital life. She was first seen on March 20, 1947, with complaint of "growth on

right side and question of pregnancy." Last menstrual period was Dec. 22, 1946, the expected date of confinement being Sept. 28, 1947. Examination revealed slight tenderness in the left lower quadrant. The fundus was palpable 1 cm. above the symphysis pubis and deflected to the right. Pelvic examination revealed marked mucopurulent vaginal discharge with marked vaginitis and cervicitis. The uterus was approximately 10 cm. in diameter deflected to the right. In the left adnexal region a soft, slightly tender, tubular mass was felt. Smears revealed numerous pus cells, staphylococci and streptococci. No gonococci were found. A diagnosis of pregnancy, three months' duration, marked nonspecific vaginitis and cervicitis with left hydrosalpinx was made. A marked improvement of the vaginal discharge followed administration of sulfadiazine orally and penicillin by intravaginal suppositories. Except for occasional discomfort in the left lower quadrant, the subsequent course was uneventful. X-ray pelvimetry on Aug. 28, 1947, revealed a platypellic pelvic with anteroposterior diameter of inlet measuring 10.1 cm. with a transverse diameter of 14.2 cm. Outlet: Bituberous, 7½ cm.; anterior sagittal, 4 cm. A single unengaged vertex was noted. The placenta was not visualized.

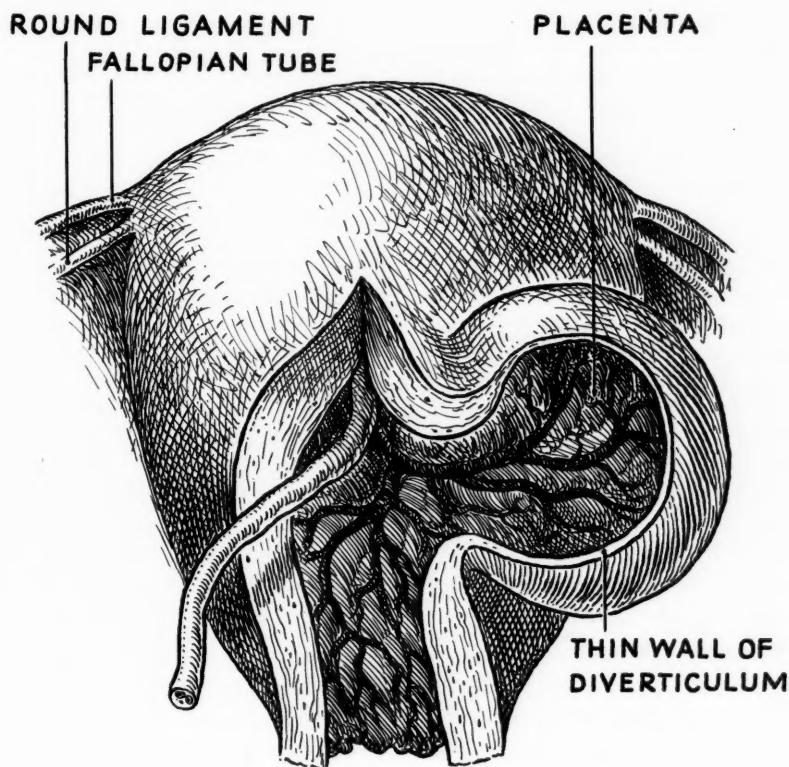


Fig. 3 (Case 2).—Diverticulum of anterolateral wall of uterus.

On examination on Sept. 23, 1947, the patient complained of vague sensation of pressure in the pelvis and the uterus was felt to be unusually tense. She was admitted to the New Haven Hospital on Sept. 24, 1947. Temperature was 98° F., pulse 80, respirations 20, blood pressure, 120/70, white blood cells 8,800, red blood cells 3.51 million, hemoglobin 12.5 Gm., Rh negative, Mazzini test negative. The uterus reached the ziphoid process and hydramnios was apparent. The fetal heart was heard in the right lower quadrant. The uterus was tense except for a ballooned-out, rounded, soft area on the left side of the fundus estimated at 10 cm. in diameter and contiguous with the uterine wall. The tenseness of the fundus did not

permit palpation of fetal parts. The vertex was felt to be lightly engaged. The cervix was long, soft and 1 cm. dilated. In view of the findings suggestive of diverticulum, cesarean section was elected.

Under local Novocain (1 per cent) infiltration supplemented with intravenous Pentothal, a low cervical cesarean section was done through a midline suprapubic incision. The uterus was markedly enlarged but not rotated. A rounded, thin-walled, soft mass was palpated arising from the left side of the uterus. The peritoneal flap was dissected free from the lower uterine segment and the uterus incised longitudinally, the placenta being attached to the anterior wall and extending into the vicinity of the mass. Infant No. 1 presented and the feet were grasped to permit ready delivery. Infant No. 2 presented a vertex and was readily delivered. Further examination of the uterus revealed a diverticulum of the left anterior wall of the uterus, inferior to the left round ligament and anterior to the left broad ligament, estimated 8 to 10 cm. in diameter. The placenta extended into the vicinity of the thin-walled diverticulum and lack of definite cleavage plane made separation difficult, suggesting invasion of the uterine wall in this area similar to placenta accreta. After contraction of the uterus by means of Ergotrate and Pitocin, the uterine musculature in the involved area measured approximately 3 to 4 mm. in comparison with a thickness of $1\frac{1}{2}$ cm. of the adjacent uterine wall. A tendency to continued bleeding from the placental site was controlled by means of Oxyeel gauze. After intrauterine application of sulfanilamide (1 Gm.), the uterine incision was closed by means of interrupted sutures of fine chromic catgut and extraperitonealized by means of the uterovesical flap in the usual manner. Penicillin, 30,000 U., every 4 hours, intramuscularly, was given for six days. Vital signs remained normal after second post-operative day. The patient was discharged on the eleventh day. The uterus was firm, 3 cm. above the symphysis pubis, slight tenderness was present on the left. General condition excellent.

In each instance of diverticulum above described, the sac was connected with the uterine cavity by a relatively narrow neck while the wall consisted of markedly thin myometrium with strength undoubtedly further impaired by vascularization associated with the attachment of the placenta to its inner surface. The risk of rupture of such weakened areas would seem to be great, particularly when subjected to the additional strain of the expulsive forces of labor. The anatomical relationship to the cornual structures would substantiate the diagnosis of true diverticula.

Comment

It is not improbable that small diverticula having a relatively thick myometrial wall exist without recognition and labor progresses without ill-effect. Such elevated areas have been seen on the surface of the uterus at cesarean section by many operators. These require no special consideration. However, the palpation of a sizeable, ballooned-out mass contiguous with the uterine fundus and through which on occasion the fetal parts may be easily felt, should suggest the possibility of a diverticulum. Roentgen examination, using a soft-tissue technique may give additional information to support the diagnosis. In view of the danger of rupture under the stress of labor, as well as the possibility of intraperitoneal hemorrhage from an immediately underlying placenta, cesarean section should be done. In some instances, when so located as to be accessible through the abdominal incision, delivery may be effected through a uterine incision placed along one margin of the sac. After delivery of the infant and the placenta, the remainder of the sac and the deficient myometrium may be excised and the wound closed in the usual manner. In view of the uncertainty of our knowledge of the regenerative ability of the myometrium, in some in-

stances it may seem feasible to undertake no attempt at excision. If there is evidence of gross infection or alarming persistent hemorrhage after removal of an intimately adherent placenta, it may be necessary to remove the uterus, particularly when the diverticulum is so located that its excision is technically impossible. When a uterus with a demonstrated diverticulum has been left in situ, future pregnancy should receive close observation. Lipiodol studies of the uterine body would seem advisable before pregnancy is permitted.

References

1. Schickele and Freund: Beitr. z. Geburtsh. u. Gynäk., Leipz. 8: 267-293, 1904.
2. Batizfalvy, V.: Orvosi hetil. 81: 761-767, 1937.
3. DeLee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 9, Philadelphia, 1947, W. B. Saunders.
4. Stander, H. J.: Textbook of Obstetrics, 3rd revision, New York, 1945, D. Appleton-Century Company, Inc.
5. Hawkins, M. C., Jr.: AM. J. OBST. & GYNEC. 50: 562-563, 1945.

Lyons, Arthur W.: Post-Partum Hematoma, New England J. Med. 240: 461, 1949.

The material for this report was derived from Bon Secours Hospital, Baltimore, Md. A review of 1,250 vaginal deliveries revealed that there were three postpartum hematomas. The first two were vulvar in origin, requiring removal of episiotomy sutures, evacuation of the clot, and resuturing. The third was a late paravaginal hematoma, which occurred on the seventh postpartum day, seven days following the patient's discharge from the hospital.

The patient had been delivered by median episiotomy (perineotomy) and low forceps. She returned to the emergency clinic complaining of severe perineal pain. Examination revealed a hard, symmetrical mass extending 10 cm. above the pubis; a gaping infected episiotomy wound; a mass extending 7 cm. inside the vagina on the left lateral wall. The temperature was 104.4° F., the pulse 140, and respiration 22. There were 2,860,000 red blood cells and 58 per cent hemoglobin.

Treatment consisted of a blood transfusion, administration of penicillin and streptomycin, evacuation of the blood clot, and insertion of proper drainage. The patient responded satisfactorily to this therapy and was discharged. Four months later the patient was admitted for a secondary perineorrhaphy.

The author states that in a review of the literature from 1554 to 1948 he was able to collect only 188 cases of paravaginal hematoma. Many more must be unreported. The introduction of penicillin and streptomycin has almost eliminated fatalities, which formerly amounted to 8.3 and 9.5 per cent maternal mortality.

JAMES PRATT MARR.

RADICAL TREATMENT OF ABORTION

An Analysis of One Thousand Cases

H. B. SAFFORD, M.D., AND E. F. LONGWORTH, M.D., NEW YORK, N. Y.

(From the Metropolitan Hospital)

THE treatment of abortion has two main trends—the inactive, or medical, and the active surgical or radical approach. Over a period of years the radical treatment has been used almost exclusively on the gynecological service at the Metropolitan Hospital. For the purpose of the following analysis, an incomplete abortion is considered to be the interruption of pregnancy with the loss of some of the products of conception up to and including the twenty-eighth week of gestation.¹ Radical treatment is considered as a complete clearing of the uterine cavity of its contents by some mechanical method, digital curettage, the use of sponge forceps or the curette, or a combination of these methods. We do not hesitate to employ the sharp curette upon occasion, believing that its cautious use will sometimes dislodge fragments of tissue that can be recovered in no other way. We consider digital curettage, when practical, the ideal procedure.

During the period of time covered by this report, the only exceptions to the radical treatment comprised a small group of patients practically moribund when admitted to the wards and another small group in which the procedure was considered technically impractical. Elevation of temperature, rise in sedimentation rate, and other evidence of inflammatory involvement were not considered as contraindications to the method.

One of the factors which led to our adoption of the active surgical approach to the treatment was the conviction that many cases, ordinarily considered *complete* abortion, were really *incomplete* despite the absence of symptoms of bleeding or temperature. More than a few patients in this series had been previously treated elsewhere by the conservative method for either incomplete or complete abortion. The study of pathological material obtained in the operating room indicated that a high percentage still retained placental elements. Thus, in addition to the hazards of infection and hemorrhage, these patients faced the statistical risk of hydatidiform mole and chorionepithelioma which, though infrequent, are of sufficiently grave importance to warrant some consideration in any discussion on incomplete abortion.³

There seems some reason to believe that insufficient stress has been laid upon the sequelae of long-standing and inadequately treated infection due to incomplete abortion. Adequate statistics are not available on the incidence of sterility, subinvolution, fixed displacements of the uterus, chronic adnexal disease, ectopic pregnancy and a host of other conditions following incomplete

abortion to justify an authoritative statement concerning the relationship. It is our opinion that the percentage of patients with these sequelae must be considerable, with particular reference to the lengthy conservative method of treatment.

This report covers the study of one thousand cases admitted to the hospital. Since the survey was made in two parts, the data are not as complete in the older group of 346 patients as in the more recent group of 654. The analysis which has been made treats with the following points:

1. Incidence of incomplete abortion according to period of gestation: (a) spontaneous; (b) induced, either by self or by criminal agent.
2. Sedimentation rate in incomplete abortion.
3. Hemoglobin rate in incomplete abortion.
4. Use of adjuvant therapy in incomplete abortion: (a) transfusions; (b) packing; (c) sulfonamides.
5. Morbidity and mortality rates.
6. Period of hospitalization.
7. Pathologic study of tissue obtained by operative procedure.

In 654 cases the period of gestation and method of abortion were recorded. There were 519 with spontaneous abortion, or 79.4 per cent, and 135, or 20.6 per cent, with criminally or self-induced abortion. The following table shows that the total number of spontaneous abortions occurring in the sixth, eighth, twelfth, and sixteenth weeks was 219, or 42 per cent of all spontaneous cases, indicating a greater incidence at the time when menstruation would be due under normal circumstances or at the time of the second ovulation following conception. The addition of the induced cases comprising the entire 654 does not materially change the percentage.

TABLE I. DURATION OF GESTATION IN INCOMPLETE ABORTION

GESTATION WEEK	NUMBER OF CASES	PERCENTAGE OF 654
4th	20	3.0
5	20	3.0
6	72	11.0
7	40	5.1
8	90	13.5
9	51	7.6
10	49	7.3
11	55	8.4
12	83	12.7
13	40	5.1
14	15	2.3
15	20	3.0
16	38	5.1
17	17	2.6
18 and 19	9	1.4
20	11	1.5
21 to 28	17	2.6

The sedimentation rate was recorded in 657 cases. The Westergren tube method was used, but for the purposes of statistical simplicity only the one-hour reading is utilized in the following table. The average sedimentation rate was 41.9 mm. in an hour. The rate in cases of induced abortion was 52 mm., and 39 mm. in the spontaneous, indicating a moderately higher degree of infection in those induced.

TABLE II. SEDIMENTATION RATE IN INCOMPLETE ABORTION

RATE IN MM. AT END OF 1 HOUR.	NUMBER OF PATIENTS	PERCENTAGE OF 657
0-10	90	13.7
11-20	142	21.6
21-30	102	15.6
31-40	100	15.3
41-50	53	7.7
51-60	48	7.0
61-70	39	5.9
71-80	22	3.3
81-90	16	2.4
91-100	9	1.4
Over 100	34	5.3

The hemoglobin level in the blood was recorded in 683 of the 1,000 cases analyzed. The Sahli method of determination was used with 14.7 Gm. equalling 100 per cent. The readings varied from 11 to 100 per cent, with the majority falling between 50 and 90 per cent. An attempt was made to establish some correlation between the blood hemoglobin level and the morbidity rate, and it was found that morbidity was definitely affected inversely by the level of the patient's hemoglobin. If 15 per cent be considered the norm for morbidity in this series, as is shown later, it can be deduced that every attempt should be made to bring the blood level of hemoglobin to 70 per cent by transfusion, since numerically two-thirds of the morbidity occurs below this level. In effect this was our policy as illustrated later in the report where it is shown that morbid patients received two-thirds of all transfusions given.

TABLE III. HEMOGLOBIN LEVEL IN INCOMPLETE ABORTION

HEMOGLOBIN %	NO. PATIENTS	PERCENTAGE OF TOTAL RECORDED	NO. MORBID	PERCENTAGE MORBID AT EACH HEMOGLOBIN LEVEL
11-20	3	0.44	2	66.6
21-30	4	0.58	2	50.0
31-40	12	1.76	8	75.0
41-50	40	5.86	14	35.0
51-60	99	14.49	28	28.1
61-70	189	27.67	49	25.9
71-80	207	30.31	36	17.4
81-90	98	14.33	8	8.2
91-100	31	4.54	2	6.5

Although surgical evacuation of the uterine contents was the keynote in the treatment of incomplete abortion in this series, many received other treatment as well. It is this other treatment alone upon which many depend.⁴ On admission to the hospital, all patients were examined, placed on bed rest, fluids, oxytocics, and supportive therapy as indicated. In addition uterine packing, transfusion, and chemotherapy were used as the need arose, but we do not feel that these measures alone constitute an adequate substitute for emptying the uterus of the etiological agent of morbidity.

TABLE IV. USE OF PACKING AS AN ADJUVANT IN THE TREATMENT OF INCOMPLETE ABORTION

	MORBID	NONMORBID	TOTAL
Preoperative	20	88	108
Postoperative	105	298	403
Both	68	98	166
Totals	193	484	677

Uterine packing was used in 677 cases either preoperatively, postoperatively, or both. Preoperatively it was used to arrest hemorrhage until the patient could be brought to operation, but postoperatively it served mainly to bring out bits of placenta that the curette or sponge forceps may have detached and failed to evacuate.

One hundred forty patients received transfusions. All of these were packed. The effect of transfusions on morbidity could not be measured by this study because inevitably the patients selected for transfusion were also the most morbid. In a previous paragraph we have indicated the correlation. However, it is logical to assume that the ability to combat infection is enhanced by an adequate blood picture. Transfusion was used in 35 cases of induced abortion and in 105 spontaneous cases.

TABLE V. TRANSFUSIONS IN INCOMPLETE ABORTION

<i>A. In Relation to Morbidity.—</i>				
	MORBID PREOP.	MORBID POSTOP.	NONMORBID	TOTAL
Preoperative	31	17	39	87
Postoperative	12	12	5	29
Both	16	8	0	24
Totals	59	37	44	140
<i>B. In Relation to Packing.—</i>				
	PREOP. PACK	POSTOP. PACK		TOTAL
Preop. transfusion	34	44		78
Postop. transfusion	12	20		32
Both	15	15		30
Totals	61	79		140

Since this report covers a period prior to the unrestricted use of penicillin in New York City hospitals, in the majority of cases the adjuvant bio- or chemotherapy was restricted to the use of sulfonamides. A total of 206 cases received sulfonamide therapy and of these 143 were morbid.

TABLE VI. SULFONAMIDE ADJUVANT THERAPY IN INCOMPLETE ABORTION

	NONMORBID	MORBID PREOP.	MORBID POSTOP.	TOTAL
Sulfonamide preop.	33	83	10	126
Sulfonamide postop.	30	36	14	80
Totals	63	119	24	206

Morbidity rates were analyzed using a standard of 100.6° F. rectal temperature appearing on any two successive days throughout the hospital stay. A comparison of the gross morbidity before and after operation did not show any marked increase due to the active surgical treatment. The net increase in morbidity due to the treatment or coincidental with it amounted to 2.6 per cent, or 26 cases in the thousand. Most of the patients who were morbid before operation remained so for a period of time postoperatively. There were three deaths among the patients treated, but the corrected mortality rate was one in the thousand, or 0.1 per cent. The immediate cause of death in the two cases which were excluded in calculating the mortality rate was pulmonary tuberculosis, the incomplete abortions having been certified as a contributory cause of death even though the demises occurred seventy and one hundred forty-two days postoperatively.

TABLE VII. MORBIDITY RATES IN THE ACTIVE SURGICAL TREATMENT OF INCOMPLETE ABORTION (1000 CASES)

Total number morbid preop. but not morbid postop.	29	or	2.9%
Total number morbid postop. but not preop.	26		2.6
Total number morbid both preop. and postop.	95		9.5
Morbidity rate			15.0

The average period of hospitalization for patients treated by this active surgical method was 8.5 days. This is a longer period than reported by Morse for the active treatment, but shorter than the average for those treated by the conservative method, as reported by Russel³ and others. Since 80 per cent of our cases did not come to operation within forty-eight hours after admission, it seems probable that the duration of the hospital stay might have been lowered by the elimination of this delay.

TABLE VIII. PERIOD OF HOSPITALIZATION

Total patient days in the hospital for 1,000 patients	8540
Average period of preoperative hospitalization	4.2 days
Average period of postoperative hospitalization	4.3 days
Average total period of hospitalization	8.5 days

TABLE IX. PRE- AND POSTOPERATIVE HOSPITALIZATION

A. PREOPERATIVE HOSPITALIZATION		B. POSTOPERATIVE HOSPITALIZATION	
Operation day of admission	0.2%	1 day hospital stay	0.1%
Operation 1st day	1.1%	2 days' stay	0.7%
Operation 2nd day	20.5%	3 days' stay	40.6%
Operation 3rd day	25.4%	4 days' stay	29.6%
Operation 4th day	16.4%	5 days' stay	10.2%
Operation 5th day	7.9%	6 or more days' stay	18.8%
Operation after 5th day	28.5%		

All operative specimens were subjected to microscopic examination by the pathological laboratory. The series of 1,000 cases is divided into two groups for statistical purposes because in the first group of 346 patients no differentiation was made between decidual tissue and chorionic villi by the laboratory, positive findings in either case being reported as "retained placental tissue." In the more recent group of 654 patients such differentiation was made.

In the earlier group of 346 cases, 324 were reported as "placental tissue," and 22 either had no report, were incorrectly diagnosed, or were cases of true complete abortion. We shall consider these 22 cases among the diagnostic errors for statistical purposes in this report. In the later group, decidua alone was reported in 43 per cent, chorionic villi in 55 per cent, no pathological report was found in 0.4 per cent and 1.6 per cent were incorrectly diagnosed as abortion before operation. The pathological reports for the cases incorrectly diagnosed included normal interval endometrium in two instances, endometrial hyperplasia in nine, interstitial endometritis in six, carcinoma of the cervix in one, blood clot in one, and polypoid endometritis in one. The over-all diagnostic error for the thousand cases was 4.2 per cent.

By interpolation of the available figures, the analysis of the series shows that the laboratory examination of the surgical specimens proved true incomplete abortion, i.e., the existence of chorionic villi in the uterus, in over half (55 per cent) of the cases, while the presence of either chorionic villi or decidua alone was found in 95 per cent. This high correlation suggests the advisability of considering and treating all abortion cases as incomplete, especially in view of

the fact that many cases showing the findings of retained decidua alone bleed sufficiently to warrant surgical interference on this indication.

TABLE X. MICROSCOPIC FINDINGS AT PATHOLOGICAL EXAMINATION

	DECIDUA	CHORIONIC VILLI	WRONG DIAGNOSIS	NO REPORT	TOTAL
346 cases (earlier series)	324 or 93.6%		22 or 6.4%	0	436
634 cases (later series)	275 or 43 %	353 or 55%	20 or 1.6%	6 or 0.4%	654
1,000	952 or 95 %		42 or 4.2%	6 or 0.6%	1,000

Summary

One thousand cases diagnosed as incomplete abortion, four out of five having occurred spontaneously, were treated by active surgical methods with a mortality rate of 0.1 per cent, a morbidity rate of 15 per cent, an average hospital stay of 8.5 days, and a diagnostic error of 4.2 per cent. Retained chorionic villi were demonstrated in more than half of a group of 634 cases, showing that the products of conception had not been extruded spontaneously and suggesting that complete abortion is not the usual natural termination. The sedimentation rate was found to be elevated in a majority of the cases and the hemoglobin lowered. Packing, transfusion, and sulfonamides were used as adjuvant therapy but are not considered adequate treatment for incomplete abortion because of the high incidence of retained placental elements.

References

1. Titus, Paul: *The Management of Obstetric Difficulties*, ed. 1, St. Louis, 1937, The C. V. Mosby Company, Chap. X, p. 276.
2. Morse, W. S.: *M. Rec. & Ann.* 41: 148, 1947.
3. Russel, P. B., Jr.: *South M. J.* 40: 324, 1947.
4. Maternal Welfare Committee of the Medical Society of the State of North Carolina, *North Carolina M. J.* 8: 314, 1947.

640 PARK AVENUE

Lemmon, W. M.: The Management of Delayed Response to Artificial Rupture of Membranes as a Method of Inducing Labor, M. J. Australia 2: 649, Dec. 4, 1948.

A total number of 1,113 cases were induced by this method. In this series 70.7 per cent of all patients were delivered within twenty-four hours of induction and a further 14.3 per cent within the next twenty-four hours. Cesarean section was performed in 33 cases in this series. The maternal mortality rate was 1.25 per cent. The morbidity rate for the whole series was 9.25 per cent. Delayed response to artificial rupture of the membranes markedly increases the fetal mortality rate. For the whole series this was 19.95 per cent. In 942 cases the indication for induction was some form of toxemia, the other large groups being maturity, postmaturity, antepartum hemorrhage, and hydramnios. Cesarean section had to be performed subsequently in a number of cases because of increasing toxemia. The method is considered quite safe because in the 1,113 cases there was only one maternal death which could be directly attributed to the procedure. Morbidity is increased by delay in the completion of the delivery, and serious complications may be reduced by prophylactic chemotherapy. Medicinal stimulation is a useful adjunct to artificial rupture of the membranes.

WILLIAM BERMAN.

PLEUROPNEUMONIA-LIKE ORGANISMS OF THE FEMALE GENITAL TRACT

A Study of Three Hundred Gynecologic Cases

JOHN H. RANDALL, M.D., ROBERT J. STEIN, AND JO-CAROL AYRES,
IOWA CITY, IOWA

*(From the Department of Obstetrics and Gynecology, University Hospitals,
State University of Iowa)*

WITHIN recent years, considerable attention has been given to a group of microorganisms known as the pleuropneumonia-like or L-organisms.* These organisms are filterable, may be parasitic or saprophytic, and are as yet taxonomically unclassified, but possess properties which distinguish them from bacteria, rickettsiae, and viruses. They may be grown in cell-free culture media, where they develop different types of pleomorphic elements, such as small granules, bacillary filaments, and filterable elementary bodies usually 150 to 250 millimicrons in diameter, which are thought to be the fundamental reproductive units. On suitable solid media, numerous colonies, not larger than 600 microns in diameter, develop. The colonies are tridimensional, invade the agar, and after two to five days' growth exhibit opaque centers embedded in the agar and thin peripheral zones. Though these cultural characteristics are common to both the saprophytic and parasitic strains, the latter are further characterized by their inability to grow in cultures lacking a high concentration of serum proteins.

Nocard, Roux, and others, in 1898,² first isolated an organism which is the prototype of the entire pleuropneumonia group and recognized it as the etiological agent of contagious bovine pleuropneumonia. This organism has properties similar to the viruses, being filterable and invisible in the usual microscopic preparations. In contrast to viruses, however, it can be cultivated in a cell-free culture medium. Bridre and Donatien,³ in 1923, discovered an organism with similar properties which is the cause of agalactia in sheep and goats. This disease is characterized by inflammatory involvement of joints, eyes, and lactating mammary glands. A serologically distinct species of this group has been isolated from dogs,⁴ but has not been established as the cause of any naturally occurring disease. Similar microorganisms have been demonstrated by Klieneberger⁵ to be the cause of spontaneous "polyarthritides" in rats. Perhaps the most significant discovery has been the detection of the L-forms in cultures of various bacteria.⁶

The natural occurrence of distinct species of the pleuropneumonia group in man has been demonstrated beyond doubt. In 1937, Dienes and Edsall⁷ for the first time cultured organisms belonging to the pleuropneumonia group from

*Klieneberger⁴ employed the letter "L" to identify the different strains of pleuropneumonia organisms she isolated.

human beings.* Since then, their presence in the male and female genitourinary tract has been reported by a number of investigators.⁹ The incidence of L-forms in the female has been studied by Klieneberger,¹⁰ Beveridge,¹¹ Salaman,¹² Dienes,¹³ and Dienes and Smith,¹⁴ who found the organism in both normal and diseased genital tracts.

TABLE I. INCIDENCE OF PLEUROPNEUMONIA-LIKE ORGANISMS FOUND IN THE FEMALE GENITAL TRACT BY VARIOUS INVESTIGATORS

AUTHOR	CLINICAL DIAGNOSIS OR SOURCE OF SPECIMEN	NUMBER OF CASES	NUMBER WITH L-FORMS	PER CENT
Dienes and Edsall (1937) First human isolation	Bartholin's abscess	1	1	100
Dienes and Smith (1942) Consecutive series of cultures from unselected cases.	Cervical cultures	77	23	29
Klieneberger (1945)	Discharge Growths, cysts, etc. Irregular menses Vulvitis, cervical erosion Pelvic infection Pregnancy and abortion No gynecologic disease Venereal disease	8 6 6 3 3 7 3 45	6 2 1 0 0 2 1 18	33 40
Salaman (1946) Smears taken from cervix, urethra, or both.	Trichomonas vaginitis Nonspecific cervicitis Nonspecific cervicitis and trichomonas vaginitis Venereal disease Clinically normal women	63 18 8 38 17	39 8 6 31 1	59 81 6
Beveridge (1948)	Erosion of cervix "Apparently normal women"	11 101	3 7	27 6
Dienes and co-workers (1948) Specimens in most cases submitted for examination for gonococci.	Cervical secretion Urethral discharge (female) Bartholin abscess Salpingitis Peritonitis arising from salpingitis	214 4 6 8 4	56 0 1 1 1	26 0 17 13 25

Certain pelvic infections in women have an obscure etiology. In view of the possible clinical and pathologic significance of the L-forms, it was felt advisable to investigate the frequency and properties of these organisms in the lower genital tracts of women in an attempt to correlate certain symptoms and findings associated with their presence.

Cervical cultures from a series of 300 consecutive patients admitted to the gynecologic service were examined for the presence of pleuropneumonia-like organisms and the findings correlated with the symptoms.

Method

The cervix of each patient was clearly exposed with a speculum, and material obtained by a sterile platinum loop was immediately streaked on 10 per cent blood agar plates, 10 per cent chocolate agar plates, and Dienes¹⁵ sedimented boiled horse blood agar to which 30 per cent ascitic fluid or 20 per cent horse serum had been added. Although pleuropneumonia-like organisms are essentially aerobic, the cultures were incubated both aerobically and anaerobically. The plates were examined after three and five days. Macroscopically

*Gerlach⁸ was probably the first to suggest the presence of pleuropneumonia-like organisms in man.

visible colonies, pin-point in size, were occasionally observed but more often the growth was 10 to 30 microns in diameter and could be recognized only in microscopic preparations made by the agar-fixation method of Salaman¹² or the stained agar method of Dienes.¹⁵

1. *Salaman's Method.*—

Twenty-five millimeter squares of agar bearing L-organisms are cut out and placed face downward on slides, which are flooded with Bouin's fluid and put into a moist chamber in the incubator over night. After 24 hours, the agar is peeled off, the colonies remaining adherent to the slides, which are then immersed in 75 per cent alcohol for 30 minutes, rinsed in distilled water, stained in 4 per cent Giemsa stain solution for four hours and lightly differentiated and dehydrated in graded acetone-xylol mixtures as follows:

- a. Acetone containing 2.5 per cent xylol, 10 to 30 seconds.
- b. Acetone 2 parts, xylol 1 part, 30 seconds.
- c. Acetone 1 part, xylol 2 parts, 1 minute.
- d. Xylol, 10 minutes or longer.

The slides are removed from the xylol, shaken free of excess, and mounted at once, without being allowed to dry, in neutral Canada balsam.

2. *Dienes' Method.*—

Ten to fifteen millimeter squares of agar are cut from both the heavily and the lightly inoculated areas of the cultures, placed face upward on glass slides, covered with stained coverslips, and sealed with hot paraffin. The stained coverslips are prepared as follows: A solution containing 2.5 Gm. methylene blue, 1.25 Gm. azure II, 10 Gm. maltose, and 0.25 Gm. sodium carbonate in 100 c.c. of water is applied to the coverslips with a cotton applicator. The staining is complete in a few minutes, and in successful preparations the colonies appear dark blue while the agar is only slightly stained.

Observations

1. *Cultural Characteristics and Morphology of Pleuropneumonia-like Organisms.*—

The morphology of the colony as well as of the organism depends upon whether growth is observed on solid or liquid media and whether the examination is by dark-field or agar-fixation technique. In this investigation solid media and the agar-fixation methods were used exclusively. The criteria used to differentiate pleuropneumonia-like organisms from ordinary bacteria included not only the size of the colonies, but their tridimensional growth with penetration into the agar. Fully developed colonies exhibit dense centers which are embedded in the solid medium and are usually surrounded by paler-staining peripheral zones. (Fig. 1) Microscopically these colonies consist of plastic protoplasmic masses which contain "chromatin-like" bodies of varying sizes and shapes, and many granules or elementary corpuscles (Fig. 2). On the surfaces of fully developed colonies, the organisms usually have undergone cystlike hypertrophy and formed "large bodies" measuring from 5 to 20 microns in diameter. At first, these bodies stain well, but later they change into blebs with a foamlike structure (Fig. 3). Due to their extreme softness some of these vesicles may be distorted and pulled into filaments.

The growth into the medium, the presence of small pleomorphic organisms, the formation of "large bodies," and easy distortion clearly differentiate the pleuropneumonia-like organisms from bacteria.

2. *Incidence of Pleuropneumonia-like Organisms in Various Age Groups.*—

In the literature, no mention is made of the distribution of the L-forms in human beings according to age. In the present series, the L-form was found in all postpubertal age groups. The youngest patient was 15 years of age, and

the oldest 81. Among 127 women between the ages of 15 and 40 years, L-forms were present in 38 per cent; while in 158 patients between 41 and 70 years, the incidence was 16 per cent. There is evidently, then, a tendency for L-forms to be more common in the cervixes of younger women. In postmenopausal patients, the L-forms were seldom present unless there was vaginal bleeding.

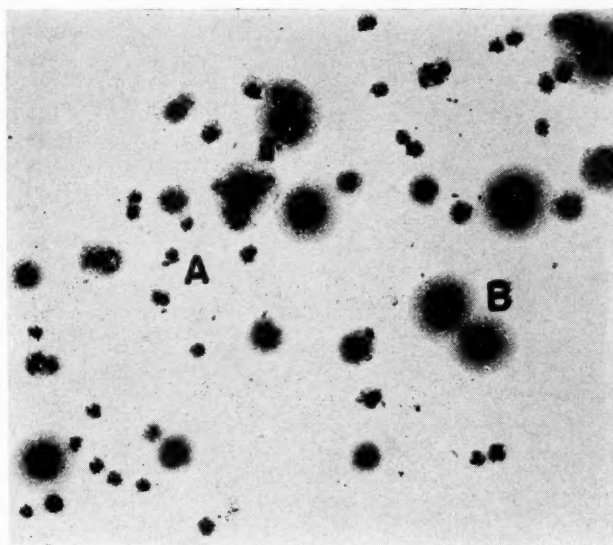


Fig. 1.—Well-developed colonies of pleuropneumonia-like organisms (A) situated among larger bacterial colonies (B). Agar-fixation followed by Giemsa staining. ($\times 100$.)

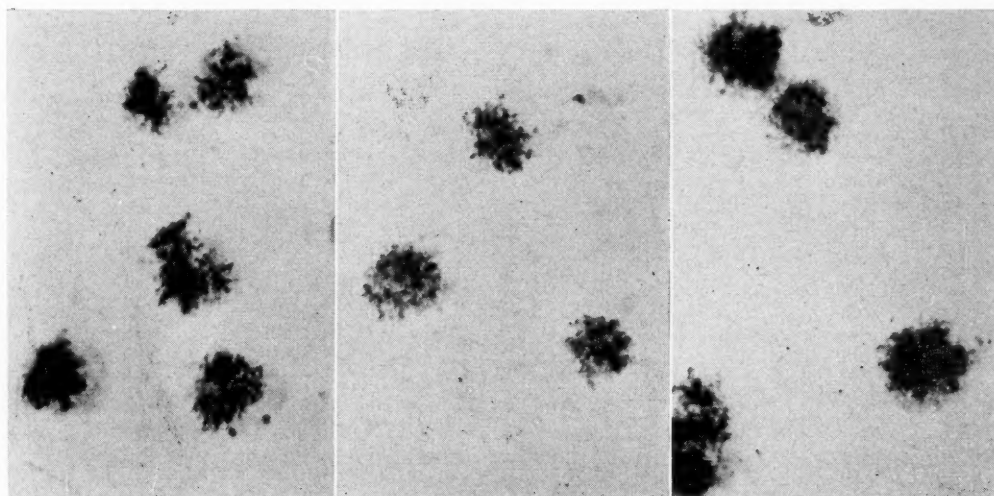


Fig. 2.—Young colonies of pleuropneumonia-like organisms isolated from uterine cervix. Colonies consist of plastic protoplasmic masses which contain round bodies of varying sizes and shapes. Impression preparation from wet-stained agar followed by Giemsa stain. ($\times 450$.)

TABLE II. INCIDENCE OF PLEUROPNEUMONIA-LIKE ORGANISMS (L-FORMS) IN VARIOUS AGE GROUPS

AGE GROUPS (YEARS)	NUMBER OF CASES	NUMBER WITH L-FORMS	PER CENT
11-20	17	11	64
21-30	50	18	36
31-40	60	20	33
41-50	56	9	16
51-60	58	11	19
61-70	44	6	13
71-80	14	3	21
81-90	1	0	0
Total number of cases	300	78	26

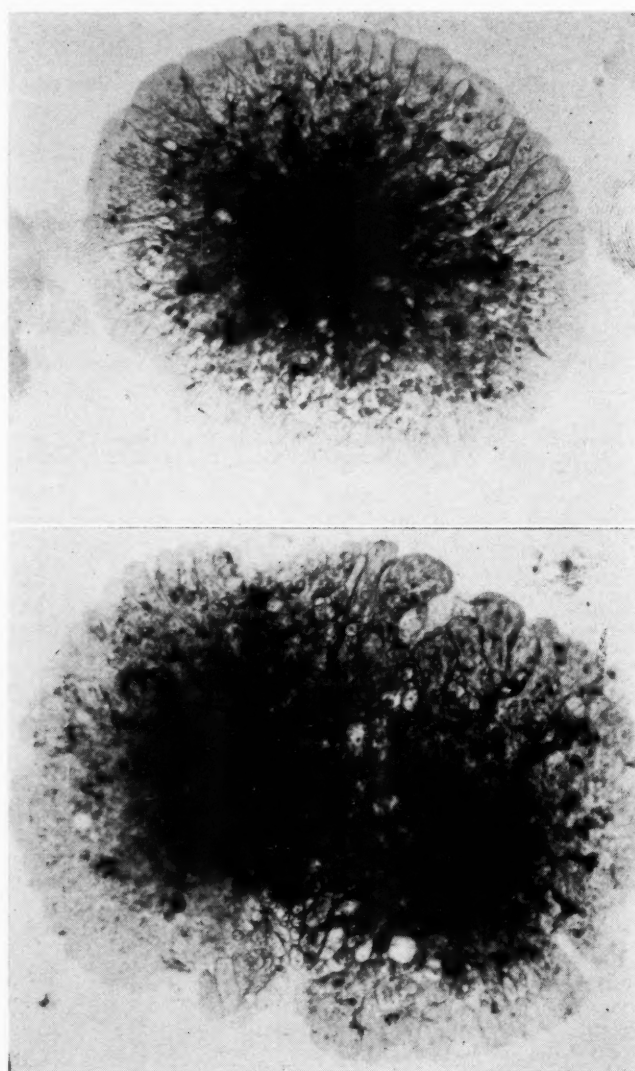


Fig. 3.—Fully developed colonies of pleuropneumonia-like organisms showing large bodies and empty vesicles produced by vacuolization of the large bodies. Agar-fixation method of Salaman, Giemsa stain. ($\times 970$.)

3. Relationship of Leucorrhea to the Frequency of Pleuropneumonia-like Organisms.—

One hundred seventy-seven patients complained of vaginal discharge, including six with lower tract gonococcal infections. Among 171 patients with nonvenereal leucorrhea, 49 revealed L-forms in culture (29 per cent), while 123 women having no noticeable discharge had 23 positive cultures (18 per cent). In six cases with lower tract gonococcal infection all cultures were positive for L-forms.

The frequency with which L-forms were found seemed to be related to the severity of the leucorrhea. Clinically moderate and severe vaginal discharges invariably yielded over 50 per cent positive cultures.

It is evident that L-forms are relatively common inhabitants of the cervix and perhaps constitute an integral part of the flora of the vagina and cervix.

4. Relationship of Bladder Symptoms to the Presence of Pleuropneumonia-like Organisms.—

Beveridge,¹¹ and Dienes and his associates,⁹ have definitely demonstrated that L-forms are implicated in urethral and bladder infections. Even though no urethral or urinary cultures were made in this series, it seemed of interest to determine if any relationship existed between bladder symptoms and positive cervical cultures.

Among 76 patients with signs and symptoms of cystitis, there were 26 positive L-form cultures (34 per cent), while 224 women without any urinary bladder symptoms showed 52 positive cultures (23 per cent). The fact that L-forms may be present in both the urinary and the genital tracts suggests the possibility of so-called nonspecific urethritis and cystitis in women being caused by this organism.

5. Pleuropneumonia-like Organisms in Women Having Noninflammatory and Inflammatory Diseases of the Genital Tract.—

The series of 300 women can be divided into two groups, those having inflammatory genital lesions and those having either noninflammatory lesions or normal pelvic organs. The group with inflammatory lesions (76 cases) had 39 (51 per cent) positive cultures for L-forms.

Two hundred twenty-four patients with no demonstrable evidence of genital tract infection revealed 39 (17 per cent) positive cultures. L-forms were found in five out of 28 women with apparently normal pelvic organs.

TABLE III. PLEUROPNEUMONIA-LIKE ORGANISMS IN WOMEN HAVING NONINFLAMMATORY DISEASES OF THE GENITAL TRACT

CLINICAL DIAGNOSIS	NUMBER OF CASES	NUMBER WITH L-FORMS
Benign neoplasms	20	3
Malignant neoplasms	66	11
Prolapse and relaxation	49	6
Functional bleeding	32	8
Polypi (cervical and endometrial)	15	4
Pregnancy	5	0
Normal pelvic organs	28	5
Others	9	2
Total number of cases	224	39
Per cent incidence of L-forms	17	

In view of the fact that L-forms occur more frequently in association with inflammatory lesions and of the evidence presented by Dienes and others that these organisms may be the sole etiological agent in certain infections, a case report is presented to substantiate the possible pathogenic nature of the pleuropneumonia-like organisms.

TABLE IV. PLEUROPNEUMONIA-LIKE ORGANISMS IN WOMEN HAVING INFLAMMATORY DISEASES OF THE GENITAL TRACT

CLINICAL DIAGNOSIS	NUMBER OF CASES	NUMBER WITH L-FORMS
Chronic pelvic inflammatory disease	10	3
Acute pelvic inflammatory disease	8	5
Pelvic abscess	3	2
Infected abortions	12	6
Cervicitis	27	15
Trichomonas vaginitis	11	6
Bartholin abscess	3	1
Vulvar abscess	2	1
Total number of cases	76	39
Per cent incidence of L-forms	51	

CASE REPORT.—R. B., 47-14687, aged 30 years, gravida 0, was admitted to the University Hospital Dec. 16, 1947. She began having lower abdominal pain and fever on Dec. 7, 1947. Examination revealed a tender mass in the left lower quadrant of the abdomen extending four fingers above the symphysis. The lower genital tract seemed normal. The body of the uterus was displaced to the right and anteriorly by a cystic mass filling the cul-de-sac and the left lower quadrant. The temperature was 102.2° F. on admission and the leucocyte count 18,700. A diagnosis of tubo-ovarian abscess was made and penicillin was given intramuscularly, 50,000 units every three hours. On Dec. 18, 1947, the cul-de-sac was needled and frank creamy pus obtained. The mass was drained through the posterior fornix and 300 c.c. of pus were evacuated. Following surgical drainage, the penicillin dosage was increased to 100,000 units every three hours, and streptomycin, 250,000 units every three hours, was given. Postoperatively, the temperature varied from 100° to 101° F. for five days and returned to normal on the eleventh day. The pus from the abscess yielded a pure culture of L-forms (Fig. 4). The patient was given pelvic heat treatments and was discharged on Jan. 23, 1948, having some residual asymptomatic inflammatory induration in the cul-de-sac. She returned to the hospital on May 29, 1948, having had no symptoms since discharge. Examination revealed a golf-ball-sized mass in the cul-de-sac which was needled. The serosanguineous fluid obtained yielded a pure culture of *Bacteroides*.

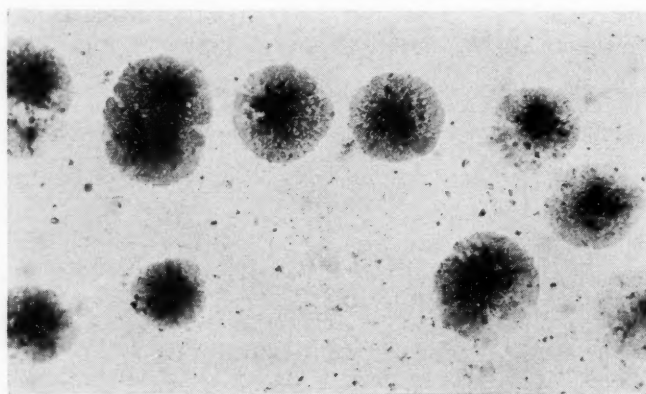


Fig. 4.—Pleuropneumonia-like colonies isolated in pure culture from pelvic abscess (Case No. 47-14687). Agar-fixation method of Salaman, Giemsa stain. ($\times 450$.)

Discussion

The common occurrence of pleuropneumonia-like organisms in the genital tracts of women shown by previous investigators has been confirmed and extended. However, the one important fact which remains to be determined is

the pathogenicity of these organisms in the human female. The reports by Dienes⁹ and his co-workers clearly indicate that in the male the L-forms are pathogenic and are etiological agents in Reiter's syndrome characterized by rheumatoid arthritis, conjunctivitis, and urethritis, and in cystitis. To quote Dienes, "The evidence of pathogenicity gained from the study of female patients is more equivocal." The high incidence of pleuropneumonia-like organisms found in women would suggest that they are either saprophytes or potential pathogens, which under proper conditions may become virulent. The greater frequency of these organisms in the presence of inflammatory processes would suggest that they may at times be pathogenic. This could be substantiated by additional isolations of pleuropneumonia-like organisms in pure culture from pelvic abscesses, as in the tubo-ovarian abscess here recorded.

When one attempts to evaluate the data presented in this study, it must be realized that in all probability there is more than one strain of pleuropneumonia-like organisms possessing different degrees of pathogenicity and that the present methods of isolation and identification probably miss many strains of L-forms.

Another difficulty in the evaluation of the pathogenicity of pleuropneumonia-like organisms is their appearance as L-variants of other organisms, such as, *Streptobacillus moniliformis*, *Hemophilus influenzae*, bacteroides, *Escherichia coli*, *Neisseria gonorrhoeae*, proteus, and, in all probability, many other bacteria. It has been shown by Dienes^{15, 16} that by the addition of penicillin to seeded cultures, many of the above organisms develop L-variants and that during penicillin therapy these pleuropneumonia-like organisms are more frequently isolated from diseased human beings. In one case (L. W., 46-1301) of lower tract Neisserian infection, cultures taken before penicillin administration were positive for *Neisseria gonorrhoeae* but negative for L-forms, whereas after this therapy L-forms were isolated in great abundance.

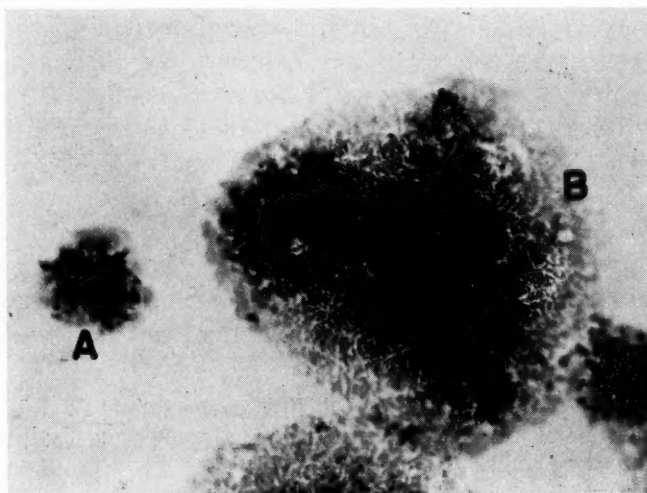


Fig. 5.—Colonies of pleuropneumonia-like organisms (A) with colonies of gonococci (B). Isolated from uterine cervix after penicillin therapy for lower tract Neisserian infection (Case No. 46-1301). Agar-fixation method of Salaman, Giemsa stain. ($\times 970$)

CASE REPORT.—The patient, a white girl, aged 15 years, was admitted to the hospital on Feb. 16, 1948, complaining of vaginal discharge and lower abdominal pain of one month's duration. The menstrual periods had been normal; the last period began one week before admission.

Examination revealed the lower abdomen to be moderately tender. Pus could be expressed from the urethra and there was an acute cervicitis with a mucopurulent discharge coming from the canal. The uterus was anterior and the left adnexa were slightly thickened and tender. Cervical cultures were positive for *Neisseria gonorrhoeae*, but those from the cervix and uterine cavity were negative for L-forms. Beginning on February 25, the patient received penicillin intramuscularly, 100,000 units every three hours, for thirty-six hours. Cultures after penicillin therapy were repeatedly negative for *Neisseria gonorrhoeae* but were positive for pleuropneumonia-like organisms (Fig. 5). The patient promptly became afebrile and symptomless, and was discharged on March 5, 1948, without palpable pelvic disease.

It is interesting to note that among thirty-four penicillin-treated women, twenty-four (70 per cent) positive cultures of L-forms were obtained. These observations apparently support Dienes' criticism that the L-forms Salaman found in his series were not true pleuropneumonia-like organisms but L-variants produced by penicillin.

The fact that many pyogenic processes do not resolve under antibiotic administration or chemotherapy and that so-called "sterile" cultures are obtained by routine bacteriologic methods suggests that in such instances there may be an L-variant or a strain of pleuropneumonia-like organism which is penicillin resistant and is itself pathogenic.

Summary

Pleuropneumonia-like organisms were present in the cervixes of 78 among 300 consecutive gynecologic admissions (26 per cent). The organisms were found in all age groups (15 to 81 years), but were more common in younger patients (15 to 40 years).

Pleuropneumonia-like organisms were found more frequently in patients with leucorrhea (177 cases) with the incidence higher in moderate (55 per cent) and severe cases (71 per cent). All patients (six) with lower tract *Neisserian* infections were positive for L-forms. In 76 cases of cystitis, 34 per cent of the cervical cultures showed L-forms.

Cervical cultures from women with noninflammatory genital lesions (224 cases) showed an incidence of 17 per cent (39 cases) of positive L-forms, and cultures from those with inflammatory lesions (76 cases) an incidence of 51 per cent (39 cases).

A case is presented (tubo-ovarian abscess) from which a pure culture of pleuropneumonia-like organisms was isolated from the pus evacuated surgically from the abscess cavity. It is suggested that the L-forms may here have been pathogenic and etiological.

L-variants due to penicillin are discussed, and a case of gonococcal pelvic inflammatory disease is reported from which L-forms were isolated after penicillin therapy.

From the evidence presented, it is clear that pleuropneumonia-like organisms are common inhabitants of the vagina and cervix, but that their role as pathogens in women needs further investigation.

References

1. Klieneberger, E.: J. Path. & Bact. **40**: 93, 1935.
2. Nocard, Roux: Ann. Inst. Pasteur **12**: 240, 1898.
3. Bridre, J., and Donatien, A.: Ann. Inst. Pasteur **39**: 925, 1925.

4. Sabin, A. B.: *Bact. Rev.* 5: 1, 1941.
5. Klieneberger, E.: *J. Hyg.* 40: 204, 1940.
6. Dienes, L.: *J. Bact.* 44: 37, 1942.
7. Dienes, L., and Edsall, G.: *Proc. Soc. Exper. Biol. & Med.* 36: 740, 1937.
8. Gerlach, F.: *Wien. Klin. Wchnschr.* 50: 1603, 1937.
9. Dienes, L., Ropes, M. W., Smith, W. E., Madoff, S., and Bauer, W.: *New England J. Med.* 238: 509, 1948.
10. Klieneberger-Nobel, E.: *Lancet* 2: 46, 1945.
11. Beveridge, W. I. B.: *M. J. Australia* 2: 479, 1943.
12. Salaman, M. H.: *J. Path. & Bact.* 58: 31, 1946.
13. Dienes, L.: *Proc. Soc. Exper. Biol. & Med.* 44: 468, 1940.
14. Dienes, L., and Smith, W. E.: *Proc. Soc. Exper. Biol. & Med.* 50: 99, 1942.
15. Dienes, L.: *J. Infect. Dis.* 65: 24, 1939.
16. Dienes, L.: *Proc. Soc. Exper. Biol. & Med.* 64: 166, 1947.
17. Dienes, L.: *J. Bact.* 56: 445, 1948.

Gillman, J., Gilbert, C., Gillman, T., and Spence, I.: A Preliminary Report on Hydrocephalus, Spina Bifida and Other Congenital Anomalies in the Rat Produced by Trypan Blue, South African J. M. Sc. 13: 47, 1948.

Subcutaneous injections of trypan blue were given to 100 female rats at weekly intervals. In 118 litters comprising 697 offspring, 134 (19.2 per cent) of the pups had congenital abnormalities, which were most commonly hydrocephalus, spina bifida, and eye defects, but also harelip and cleft palate, ear defects, and limb and tail defects. In the group of rats receiving injections during pregnancy only, 6 of 186 pups showed defects, and these were offspring of mothers treated on the eighth or ninth day of pregnancy. In a second group, rats were injected before conception and during pregnancy, and the incidence of congenital abnormalities rose to 65 to 80 per cent in those litters the mother of which had been injected on the sixth or seventh day before conception and on the seventh or eighth day of pregnancy. The seemingly normal offspring showed retarded growth, and after interbreeding, the second generation showed a high incidence of jaundice.

Trypan blue persists in the tissues for weeks after injection. It does not traverse the placental barrier. It is selectively adsorbed by plasma albumin, and it alters the plasma proteins and the blood picture. Thus its administration mimics a metabolic disorder (virus infection, biochemical disturbance, malnutrition) in its possible relationship to the pathogenesis of congenital defects.

The authors review critically the known facts concerning maternal rubella. It is doubtful that the virus can cross the placenta to affect the fetus directly. The authors suggest that the virus affects maternal proteins, impairing cellular metabolism in a manner quite analogous to that of trypan blue. The phenomena of critical periods of organ vulnerability, and the pre-conception insult having a later fetal effect, are present in both instances. If the mechanisms of damage by trypan blue, and by rubella virus are quite similar, a seemingly normal child born after maternal rubella would bear close watching.

This technique for the study of the pathogenesis of congenital defects is said to be more controllable, specific, and prompt than external x-radiation (variable in effect, and affects maternal tissues) or nutritional experiments (prolonged and difficult to control adequately).

IRVING L. FRANK,

II. THE INFLUENCE OF STILBESTROL ON SERUM BETA-GLUCURONIDASE IN WOMEN FOLLOWING PARTURITION*

WILLIAM H. FISHMAN, PH.D.,† LESTER D. ODELL, M.D., JOHN E. GILL, M.D.,
AND R. A. CHRISTENSEN, M.D., CHICAGO, ILL.

(From the Departments of Surgery and Biochemistry, and Obstetrics and Gynecology, the University of Chicago, and the Chicago Lying-in Hospital)

INTEREST has developed in the levels of the enzyme, b-glucuronidase, in human blood serum. Fishman¹ found, using the hydrolysis of menthol glucuronic acid as the basis of his assay,² that increased b-glucuronidase activity in the blood plasma of women could be demonstrated in the last trimester of pregnancy. Following parturition, the plasma level returned to lower levels. The enzyme was also studied in the cellular components of the blood, which, although showing some elevation, did not change markedly after parturition. McDonald and Odell,³ using the hydrolysis of phenolphthalein glucuronide⁴ as their index of enzyme activity, demonstrated a progressive rise in the serum b-glucuronidase activity, which fell from high levels following parturition. In other observations made by Odell and McDonald,⁵ it was established that unusually high levels of serum b-glucuronidase frequently occurred in pregnant women, many of whom proceeded to develop toxemia of pregnancy. The detailed study of the characteristics of the variations in serum b-glucuronidase, with the events of normal and abnormal pregnancy, is the subject of an extensive investigation by Odell and Fishman.⁶

These findings of elevated b-glucuronidase in pregnancy, together with the known presence in the urine of increased amounts of steroid glucuronides, has provided additional suggestive support for a working hypothesis arrived at previously on the basis of animal experiments.^{2, 7} It was postulated that the enzyme may participate in the conjugation of steroid hormones with glucuronic acid, the complex representing, perhaps, the form in which the hormone exerts its physiological action. Other possibilities have also been suggested to explain the function of b-glucuronidase. According to experiments of Fishman and co-workers,⁸ and Friedenwald and Becker,⁹ a role of the enzyme in mucin metabolism seems indicated. According to Kerr, Levvy, and Campbell,^{10, 11} the enzyme functions only hydrolytically in processes, not yet defined, concerned with cell proliferation.

It seems desirable to investigate further the influence of estrogenic hormones on the serum glucuronidase. For this purpose, women, post partum, were divided into groups, one (nursing and nonnursing mothers) receiving no medication, and the other, a group of nonnursing mothers, receiving stilbestrol. The

*Aided by a grant from the Otho S. A. Sprague Memorial Foundation.

†Now at the Laboratories of the Cancer Research and Cancer Control Unit, Tufts College Medical School, Boston, Mass.

variations in enzyme activity were followed for ten days post partum. In the stilbestrol-treated women, the elevated serum glucuronidase was observed to persist close to the level determined at full term.

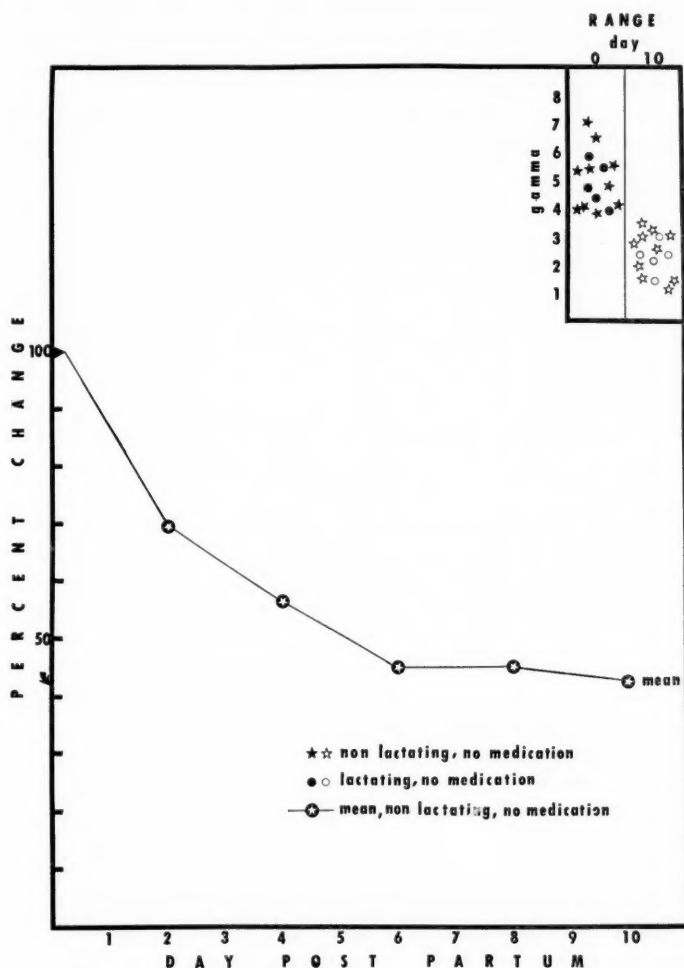


Fig. 1.—Serum b-glucuronidase in postpartum women not receiving medication.

Experimental

Serum b-glucuronidase was determined according to the method of Fishman and associates⁸ at term and every two days after parturition until the end of the ten-day period. The full-term value was taken to be 100, and the values determined post partum have been expressed in terms of percentages of the full-term figure. Ten women were in the group whose breasts were bound and who received no medication, and five were in a group who were permitted to nurse the infants but who likewise received no medication. As there did not appear to be any differences in the values determined for these two groups of patients, they have been pooled and are plotted in Fig. 1. Thirteen other women were given stilbestrol. Five of the women received 5 mg. daily for five days, and eight of them received 25 mg. daily for ten days. Their glucuronidase values have been averaged and plotted in Fig. 2. It is readily seen that the

serum glucuronidase in the group of women not treated with stilbestrol falls to 50 per cent of the initial value by the fifth day and, thereafter, remains unchanged. In the stilbestrol-treated women, on the other hand, there is a very gradual decline in the serum glucuronidase, reaching a value of approximately 80 per cent of the initial one at the end of ten days.

In Table I, are listed data obtained on normal men and women for purposes of comparison.

TABLE I. SOME DATA ON SERUM B-GLUCURONIDASE IN MEN AND WOMEN

SUBJECTS	NUMBER	AVERAGE VALUE AND	
		DEVIATION	RANGE
Men	28	162 \pm 52	45-319
Nonpregnant, adult women	54	151 \pm 49	42-316
Postmenopausal women	11	213 \pm 24	127-278
		Individual values	
Primary ovarian failure	3	263, 142, 148	
*R. T., young adult woman	1	141 \pm 47	62-275
*M. T., young adult woman	1	135 \pm 29	51-196
*B. T., young adult woman	1	145 \pm 45	62-311
*C. B., young adult woman	1	151 \pm 44	51-283

*Glucuronidase determinations were done once a week for five months.

Discussion

In discussing the possible significance of these results, one must remember that the female organism in the two weeks after parturition must be in a physiologically violent, transition state. Accordingly, the results should be interpreted with caution, against a background of relatively unknown hormonal and tissue metabolic changes.

Serum b-glucuronidase levels ordinarily do not correlate specifically and exclusively with the extent of estrogen metabolism. Thus, similar values for serum b-glucuronidase have been found in normal men and women. Attempts to correlate serum glucuronidase activity with the events of menstruation have not been too successful. Odell, Fishman, and Hepner¹² found changes in the serum enzyme of newborn infants which showed no sex differentiation.

In pregnancy, the observations do indicate a closer association of serum b-glucuronidase levels with estrogen metabolism. Thus, in normal pregnancy the serum level becomes elevated and after parturition returns to nonpregnancy levels, events which correlate roughly with the extent of estrogen metabolism.^{1, 3} In abnormal pregnancy, where it is believed by many that estrogen metabolism becomes disordered, exaggerated derangements in serum glucuronidase have been observed.^{3, 5, 6} The correlation of abnormally elevated serum glucuronidase values in women showing pre-eclampsia with water retention⁶ has directed more attention to the possible role of b-glucuronidase in mucin metabolism. Thus, it has been known for some time that intercellular mucin can be increased by the administration of estrogenic hormones.^{13, 14, 15, 16, 17} The presence of additional tissue mucin undoubtedly would lead to tissue edema.¹⁸ This hypothetical explanation for the edema in toxemia has not been seriously considered in the past, and it is now proposed that this concept merits experimental study.

The data would seem to indicate that stilbestrol is maintaining those processes which had been under the influence of estrogenic hormones during pregnancy. Inasmuch as these elevated serum-glucuronidase values can be made to persist by stilbestrol after the uterus has expelled the placenta and fetus, one must consider nonuterine organs as the source of the serum glucuronidase in this case. In this connection, Levvy¹⁹ has observed the action of estrone on organs such as liver, kidney, etc., with an accompanying increase in glucuron-

idase. It is not possible yet to define the exact nature of the reactions which result in the formation of additional glucuronidase. Nevertheless, it is possible to conclude that (synthetic) estrogen may be one factor which can influence the level of the serum glucuronidase.

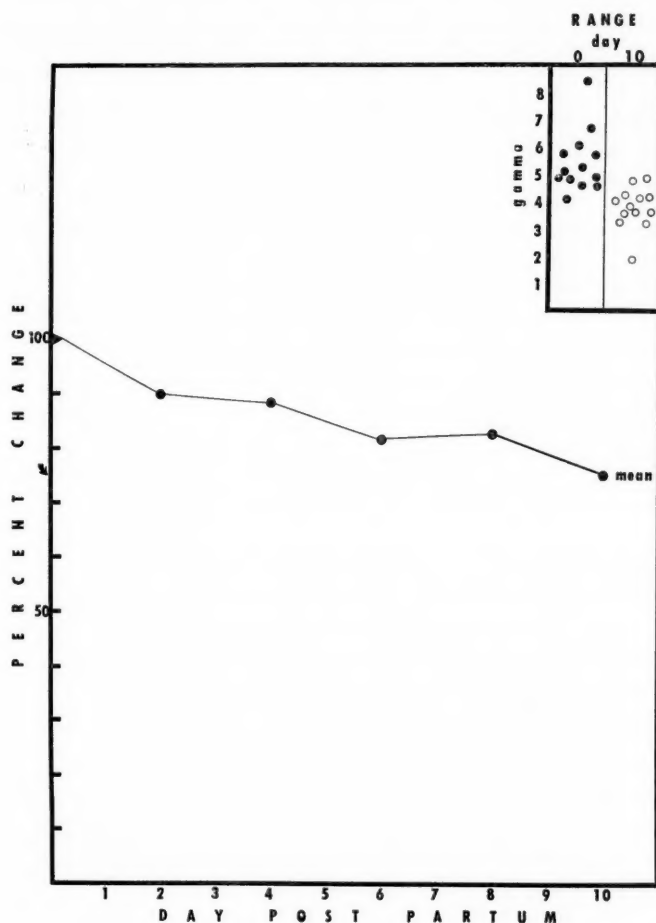


Fig. 2.—Serum b-glucuronidase in postpartum women receiving stilbestrol.

Summary

Serum b-glucuronidase determinations were made in women both at term and after parturition for periods up to ten days. In the mothers receiving no medication, the serum level drops markedly by the fifth day post partum. On the other hand, a group of mothers receiving oral stilbestrol exhibited a very gradual decline in their serum enzyme levels. The possible significance of these results has been pointed out and discussed.

References

1. Fishman, W. H.: *Science* 105: 646, 1947.
2. Fishman, W. H.: *J. Biol. Chem.* 169: 7, 1947.
3. McDonald, D. F., and Odell, L. D.: *J. Clin. Endocrinology* 7: 535, 1947.
4. Talalay, P., Fishman, W. H., and Huggins, C.: *J. Biol. Chem.* 166: 757, 1946.

5. Odell, L. D., and McDonald, D. F.: *AM. J. OBST. & GYNEC.* **56**: 74, 1948.
6. Odell, L. D., and Fishman, W. H.: In preparation.
7. Fishman, W. H., and Fishman, L. W.: *J. Biol. Chem.* **152**: 487, 1944.
8. Fishman, W. H., Springer, B., and Brunetti, R.: *J. Biol. Chem.* **173**: 449, 1948.
9. Friedenwald, J. S., and Becker, B.: *J. Cell. & Comp. Physiol.* **31**: 303, 1948.
10. Kerr, L. M. H., Levvy, G. A., and Campbell, J. G.: *Nature* **160**: 572, 1947.
11. Levvy, G. A., Kerr, L. M. H., and Campbell, J. G.: *Biochem. J.* **42**: 462, 1948.
12. Odell, L. D., Fishman, W. H., and Hepner, W. R.: *Science* **108**: 355, 1948.
13. Ogston, A. G., Philpot, J. S. L., and Zukerman, S.: *J. Endocrinol.* **1**: 231, 1939.
14. Bachman, C., Collip, J. B., and Selye, H.: *Proc. Roy. Soc. London, Series B* **117**: 16, 1935.
15. Hardesty, M.: *Am. J. Anat.* **47**: 277, 1931.
16. Sprunt, D. H. M., Dearman, S., and Rapa, J.: *J. Exper. Med.* **67**: 159, 1938.
17. Loeb, L., Sunzeff, V., and Burns E. L.: *Am. J. Cancer* **35**: 159, 1939.
18. Ropes, M. W., Robertson, W. v. B., Rossmesl, E. C., Peabody, R. B., and Bauer, W.: *Acta Med. Scandinav. Suppl.* **196**: 700, 1947.
19. Kerr, L. M. H., Campbell, J. G., and Levvy, G.: *Biochem. J.* **44**: 487, 1949.

Stefanelli, S., and Petronio, G.: Blood Level Changes of Acetylcholine at Term, During Labor, and Post Partum. Report on Placental Acetylcholine, Folia gynae. 43: 323, 1948.

The action of choline and its ester, acetylcholine, plus the high content of acetylcholine in the placenta is the basis for the authors' belief that acetylcholine may play a significant role in labor. Chang and Wong were able to induce labor with acetylcholine in 1 mg. doses every two hours in 43 per cent of cases and in 100 per cent of cases with ruptured membranes according to the authors, but, because of obviously incomplete data, these figures are most unreliable. These same investigators have also contended that acetylcholine is increased in abortions and premature separation of the placenta, while it is decreased in inertia and prolonged labor.

In reviewing the literature, the authors claim that the discrepancies noted in the serum levels of acetylcholine are attributable to the different assay methods, both biological and chemical, and to the action of acetylcholinesterase. According to Minz and Kwiatowski, the dorsal muscle of the blood sucker reacts specifically to acetylcholine and this effect is not altered in the presence of histamine, Adrenalin, Pituitrin, and other biologicals.

This paper deals with a determination of the acetylcholine content of the placenta at term, and of the blood acetylcholine level at term, at the expulsive phase of labor, and at the seventh to tenth postpartum days. The method of extraction was after that of Chang and Gaddum. For the biological assays, eserinizd dorsal muscle of the blood sucker was used.

In a study of eleven normally pregnant women, the following interesting data were obtained: The average amount of acetylcholine in milligrams per liter of blood was 18 mg. at term, 56 mg. at the end of the second stage of labor, and 35 mg. during the eighth to tenth postpartum days. The average for the placenta in each case was 24 mg. per 500 grams of placenta.

The authors conclude that acetylcholine plays an important role in the physiology of labor. They believe that it is significant as a regulating mechanism. While they admit that a good portion of it is an effect rather than a cause of uterine contractions, they believe that enough of it is elaborated by the placenta to help initiate labor.

ANDREW A. MARCHETTI.

OVULATION AND POSTOVULATION PAIN

DANIEL J. MCSWEENEY, M.D., AND ROBERT J. FALLON, M.D., BOSTON, MASS.

(From the Obstetrical and Gynecological Service of the Boston City Hospital and the Department of Obstetrics of the Boston University Medical School)

MANY needless operations are performed because of pain due to ovulation and its sequelae. Although surgery may be warranted in many cases of pain due to aberrations from the physiological phenomena following expulsion of an ovum, nevertheless careful observation and critical analysis of signs and symptoms may save many patients from unnecessary operation. In women of menstrual age, for every thirteen cases of appendicitis there will be one case presenting similar symptomatology but with pain consequent to ovulation which may not require laparotomy.¹

A report from the Boston City Hospital in 1940¹ of 257 cases of pain following ovulation admitted between 1926 and 1938 evoked considerable interest in the subject. The consequent improvement in the management of these cases has prompted the following report of 358 additional cases admitted between 1939 through 1944.

Pain consequent to ovulation is of several types. The simplest form is the transitory midmenstrual pain or *Mittelschmerz*, unilateral in the lower abdomen, caused by rupture of the Graafian follicle. The more severe types are those due to peritoneal irritation caused by blood escaping from the corpus hemorrhagicum either by leakage or actual rupture or due to the presence of a corpus luteum cyst which may cause pain from intraovarian pressure or rupture and cause a fulminating episode of pain. The corpus hemorrhagicum causes pain in the latter part of the cycle while pain from a corpus luteum cyst may occur at any time and even cause a delayed period with symptoms suggestive of a tubal pregnancy.

Novak² has emphasized the frequency of hemorrhage into the follicular apparatus. Expulsion of the ovum occurs with little or no bleeding into the abdominal cavity or into the lumen of the follicle. Thereupon, there follows a stage of hyperemia marked by a great increase in the size and number of the vessels in the theca and the base of the granulosa with subsequent bleeding into the follicle and the formation of the corpus hemorrhagicum. The latter, as a rule, contains but a small amount of blood, is well sealed off, and causes no symptoms. However, if the bleeding is excessive the corpus hemorrhagicum may rupture or the stigma fail to close, thus allowing blood to enter the peritoneal cavity and cause pain. With continued formation of the corpus luteum a large hematoma may form which may rupture and cause pain or the blood may be gradually absorbed, leaving a pain-producing corpus luteum cyst.

Material

This series of 358 cases of acute abdominal pain following ovulation complements the previous report of 257 cases and is reported to emphasize again the importance of ovulation pain in the differential diagnosis of the acute abdominal conditions and to evaluate further the signs and symptoms.

Of the 358 cases (Table I), 87 were not diagnosed prior to operation, a 24 per cent error in diagnosis, considerable improvement over the 67 per cent error of the previous series. There were 193 cases, 54 per cent, diagnosed and not operated upon and 78 cases, 22 per cent, which were considered as possibly due to ovarian bleeding but were sufficiently severe to warrant operation. There were no cases in which only a simple ruptured Graafian follicle was found at operation in contrast to 59 cases which underwent surgery in the earlier series. There has been a marked drop in the total number of cases admitted with pain following ovulation, from 92 in 1939, an incidence of 0.44 per cent of 20,737 female admissions, to 20 in 1944, 0.12 per cent of 16,453 female admissions. We believe this discrepancy is due to better judgment on the part of the admitting surgeons and referring physicians with the diagnosis being made without hospitalization.

TABLE I. STATISTICAL REVIEW OF CASES

	1939	1940	1941	1942	1943	1944	TOTAL
Not diagnosed preoperatively							
Ruptured Graafian follicle	0	0	0	0	0	0	0
Ruptured corpus hemorrhagicum	29	14	20	10	8	6	87
Diagnosed and not operated upon							
Ruptured Graafian follicle	3	9	4	4	1	0	21
Ruptured corpus hemorrhagicum	40	51	37	21	12	11	172
Diagnosed but operation deemed necessary	20	24	15	10	6	3	78
Total per annum	92	98	76	45	27	20	358
Per cent surgical intervention	53.2	38.7	46.0	44.8	53.8	45.0	
Average days in hospital before operation	1.1	1.7	1.1	1.2	0.7	2.2	

Clinical Characteristics

Pain.—The type of pain, its location, duration, radiation, and time in the menstrual cycle are most important. The pain from simple follicle rupture is mild, short in duration, rarely radiates, and usually occurs fourteen days before the next menses. The bleeding or ruptured corpus hemorrhagicum causes pain any time within two weeks of the next period. The pain tends to localize below McBurney's point, may be periodic, and lasts for two or three days. It commonly radiates across the lower abdomen and, depending on the amount of blood expelled, may radiate down the leg, into the back, or along the rectum. The corpus luteum cyst may cause a nagging pain at any time but usually in the latter days of the cycle. With rupture the attack may be fulminating and simulate ruptured extrauterine pregnancy. To complicate the diagnosis further the corpus luteum cyst may cause a delayed period, decidua-like curettings, and a tender mass in one of the vaginal vaults.³

The pain consequent to ovulation is commonly not severe enough to necessitate immediate entry into the hospital. The majority of cases, 78 per cent, were not admitted until two or three days after the onset of the pain and the average stay in the hospital before surgery was decided upon was 1.5 days.

The site of the discomfort is more often on the right side, 88 per cent of the cases. Two-thirds of the patients with lesions in the left ovary experienced pain on the right side.

Age.—Although the ages varied from 10 to 44 years, these ovarian conditions are seen predominantly in young single women between 14 and 25 years in which age group were 80 per cent of the cases. Fifty-five per cent were between 14 and 18 years, when the vagaries of menstruation usually are first manifest.

Relation to Menses.—The onset of the attack with relation to the menstrual cycle was determined in 341 cases and occurred from the twelfth to the sixteenth day in 53 per cent. The pain began prior to the twelfth day in 12 per cent and after the sixteenth day in 27 per cent. Six cases occurred before the menarche or after only one or two periods and were diagnosed as ruptured Graafian follicles. Twenty-one had no menses or irregular menses for two or three months following a miscarriage or a full-term baby. Most of the latter group were of the severe type requiring operation.

Trauma.—A history of pain precipitated by coitus, walking, running, bending, getting out of bed, or straining was elicited in 5 per cent of the cases and aids considerably in the diagnosis. Such activities will often cause recurrence of an attack after the symptoms have subsided. Attention to such details in the history would have diminished the errors in diagnosis.

Gastrointestinal Symptoms.—There is usually anorexia and frequently nausea but very little vomiting. When the latter is present it is mild, occurs soon after the pain, and disappears rapidly in contrast to appendicitis in which the vomiting becomes aggravated with time. Diarrhea is more frequent than constipation and suggests blood in the cul-de-sac but normal bowel activity is the rule.

Previous Attacks.—Fifty-eight per cent of the ruptured follicle cases had experienced one or more previous episodes with 6 per cent in this category exhibiting fairly constant midmenstrual abdominal discomfort. Twenty-nine per cent of the ruptured corpus hemorrhagicum cases gave histories of similar attacks which helped to establish the diagnosis. One-half of the entire group presented concomitant molimina suggesting ovulation such as spotting, soreness of the breasts, or leucorrhea.

Leucocytosis.—The white cell count varied from normal to 30,000. Seventy per cent had a count of 10,000 or less. Twenty-five per cent presented counts from 10,000 to 15,000. Five per cent had counts over 15,000. The number of leucocytes has a distinct tendency to fall in a short period of time. The high counts which failed to drop suggested blood in the pelvis.

Fever.—The temperature varied from normal to 103°, with the majority, 80 per cent, being under 100° F. Old blood in the pelvis tended to keep the temperature elevated.

Pulse.—The pulse rate remained fairly constant under 100 and did not rise commensurately with the temperature. The failure of the pulse to rise during several hours' observation is of considerable value in the differential diagnosis from appendicitis. A rapid rate invariably accompanied the fulminating attacks of ruptured corpus luteum or hemorrhagic cysts.

Abdominal Examination.—There was tenderness on deep pressure throughout the whole lower abdomen particularly in the right lower quadrant even if the lesion were on the left side. Tenderness an inch or more below McBurney's point was of considerable significance. Muscle spasm and rebound tenderness were rarely evident.

Pelvic Examination.—Vaginal or rectal examination found slight to exquisite tenderness in the affected vault with occasional fullness in either fornix or the posterior cul-de-sac, depending on the amount of blood in the pelvis. A palpable, enlarged tender ovary is most suggestive. Twenty-one cases exhibited palpable masses all of which were found to be cysts at operation.

Differential Diagnosis.—Of the eighty-seven patients who were operated upon with a mistaken diagnosis (Table II) the appendix was considered the offender in 84 per cent, with pelvic inflammatory disease second in frequency of mistaken diagnosis.

TABLE II. MISTAKEN DIAGNOSES

DIAGNOSIS	CASES
Acute appendicitis	57
Subacute appendicitis	4
Chronic appendicitis	7
Recurrent appendicitis	3
Appendiceal abscess	1
Ruptured appendix	1
Pelvic inflammatory disease	10
Ectopic pregnancy	2
Ruptured spleen	1
Intestinal obstruction	1
Total	87

There were thirty-five cases of ruptured corpus luteum cyst all of which were operated upon and the diagnosis illustrated in Table III. A palpably enlarged ovary established the diagnosis in twenty-one cases. The mistakes included diverse acutely severe abdominal conditions in which immediate surgery is invariably warranted.

TABLE III. DIAGNOSIS IN CYST CASES

DIAGNOSIS	CASES
Ruptured ovarian cyst	21
Ectopic pregnancy	2
Ruptured spleen	1
Appendiceal abscess	1
Ruptured appendix	1
Acute appendicitis	9
Total	35

Discussion

Although postovulation pain might be expected to occur when there is retroversion of the uterus, prolapse of the ovaries, pelvic inflammatory disease, or other causes of passive congestion of the ovaries, these abnormalities were seldom mentioned in the histories. So it would seem that any woman, especially under 25 years of age, even with no antecedent pelvic pathology, may present this condition. Important data in the history are previous attacks of a similar character, pain initiated by trauma or exertion, and onset of the symptoms within two weeks of the next menses. Pain low in the pelvis with a tendency to radiate across the abdomen, to the back, or down the legs is characteristic. Gastrointestinal symptoms are infrequent. A normal temperature and pulse rate or failure of the pulse to rise with the temperature are significant. A tendency of the white blood cell count to fall after a few hours aids in the diagnosis. Tenderness an inch or more below McBurney's point with no spasm or rebound tenderness should point to the ovary as the source of the discomfort. The latter finding together with tenderness in either lateral fornix should clinch the diagnosis. A palpable tender ovary is pathognomonic. Culdoscopy or exploratory posterior colpotomy with inspection of the ovaries through the colpotomy wound would be of inestimable value to those schooled in these techniques.

Treatment

Surgery, of course, should be avoided if possible. All ruptured Graafian follicle and most ruptured corpus hemorrhagicum cases should escape operation.

In the latter group failure of the symptoms to subside after several hours' observation with evidence of increasing accumulation of blood in the pelvis would require laparotomy. In the unruptured cyst cases, surgical intervention depends on the intensity of the symptoms. When the larger cysts rupture, surgery is invariably necessary. At operation conservatism must prevail. A mattress suture will control the bleeding in the corpus hemorrhagicum cases. Simple excision is all that is necessary in the cyst cases. Removal of the ovary is never indicated.

Summary

1. The signs and symptoms of 358 cases of postovulation pain have been recorded and evaluated.
2. A correct diagnosis was made in 76 per cent of the cases which can be improved upon with more meticulous attention to certain details.
3. One hundred sixty-five of the cases were operated upon, in eighty-seven of which operation could have been avoided.
4. The history is more important than the physical findings with the exception of a palpable tender ovary.

References

1. McSweeney, D. J., and Wood, F. O.: *New England J. Med.* **222**: 174, 1940.
2. Novak, E.: *J. A. M. A.* **68**: 1160, 1917.
3. Israel, S. L.: *AM. J. OBST. & GYNEC.* **44**: 22, 1942.

Hepp, J. A.: Functional Uterine Bleeding, Am. Pract. 3: 361, 1949.

Before any treatment for functional uterine bleeding is undertaken, a thorough general physical examination of the patient should be made, including blood studies, as the bleeding may be due to a blood dyscrasia. A basal metabolism test should also be made. In young girls with intact hymen, a rectal examination of the pelvic organs is made. In adolescent girls with functional bleeding, desiccated thyroid is the most valuable form of endocrine therapy, especially for those with a low basal metabolic rate. Gonadotropic preparations have not proved of value in the author's experience, but progesterone may be effective. In women in the reproductive period, thyroid may also be indicated if the basal metabolism is low; progesterone may be of value. Stilbestrol in a dosage of 2 mg. three times a day for ten days may act as a hemostatic. If conservative measures do not control the bleeding, therapeutic curettage is indicated, and in some cases hysterectomy, with conservation of the ovaries, is necessary. During the menopausal years, a careful pelvic examination with diagnostic dilatation and curettage is essential to rule out cancer. Endocrine therapy is not indicated in the treatment of menopausal bleeding. If the diagnostic study shows no malignancy, either hysterectomy or radium therapy is indicated. Radium therapy, with a dosage of about 1,800 mg. hr. with the radium capsule inserted in the fundus uteri, is effective in most cases of this type. In menopausal and postmenopausal patients, bleeding may be due to prolonged estrogen therapy. Estrogen therapy should be given only on definite indications and should not be too long continued without interruption. All prescriptions for estrogen preparations given to the patients should be marked: "Do not refill."

HARVEY B. MATTHEWS.

A STUDY OF MIDPELVIC CONTRACTION

HERBERT THOMS, M.D., AND ROBERT H. WYATT, M.D., NEW HAVEN, CONN.

(From the Department of Obstetrics and Gynecology, Yale University School of Medicine)

IN DISCUSSING the clinical significance of midpelvic contraction, Thoms and Schumacher,¹ in 1944, pointed out that this type of pelvic contraction, as indicated by a shortening of the transverse diameter (interspinous) of the midplane, combined or not with shortening of the midplane anteroposterior diameter, is definitely associated with increased operative intervention in labor. At that time the results seen in the labors of 153 women whose pelvises showed midplane contraction were reported. The present report concerns itself with 167 additional instances, showing a total study of 320 pelvises.

When we use the term "midplane of the pelvis" we are considering a plane which extends posteriorly from the lower posterior surface of the symphysis through the level of the ischial spines to the lower anterior surface of the sacrum. The midplane anteroposterior diameter will have its posterior end point near the junction of the fourth and fifth sacral segments dependent upon the variation of the position and the shape of the sacrum in its relation to the pelvis as a whole. The midplane transverse diameter is the shortest distance between the ischial spines. The midplane posterior sagittal diameter is that segment of the anteroposterior diameter which lies posterior to its intersection by the transverse diameter.

The obstetrical importance of this portion of the bony pelvis has been emphasized by numerous writers since Hanson's² pioneering studies in this field, and our experience has shown itself to be quite in agreement with his statement that "the course of labor is most eventful at the line of the ischial spines, particularly in occipitoposterior positions. It is here that the cardinal movements of internal rotation and descent must occur simultaneously, while flexion must be maintained or re-established." We are also in agreement with Mengert³ who emphasizes that there can be no serious outlet contraction without a commensurate contraction of the midplane, and Groskloss, Robbins, and Moehn⁴ who point out that neither the inlet morphology nor outlet configuration offers any indication of the capacity of the midpelvis.

All of the pelvises in this series have been measured roentgenologically by the Thoms and Wilson⁵ technique. In this procedure two films are used, one showing the pelvic inlet from its superior aspect, in which the bispinous or transverse diameter of the midplane may be measured using the correction scale on the edge of the film. The other view is taken laterally and in this the midplane anteroposterior and posterior sagittal diameters may be measured. As we have previously emphasized on many occasions, these and other important pelvic measurements can be obtained accurately only by roentgenometry and such procedure should be part of the prenatal program of every primigravid woman.

An experience of nearly twenty years of such routine has convinced us that only in this way may minor changes in midpelvic relationships be discovered, changes which may have major significance.

For purposes of classification we divide the usual pelvic variations into three groups:

1. *Dolichopellic*: Pelves in which the length of the anteroposterior diameter of the inlet exceeds the transverse diameter of the inlet.

2. *Mesatipellic*: Pelves in which the anteroposterior diameter of the inlet is less than the transverse by no more than 1.0 cm.

3. *Brachypellic*: Pelves in which the anteroposterior diameter of the inlet is from 1.0 to 3.0 cm. less than the transverse diameter.

Some idea of the average diameter ranges for these groups in 500 women may be seen thus:

AVERAGE DIAMETER RANGE IN 500 PELVES⁶

	DOLICHOPELLIC (CM.)	MESATIPPELLIC (CM.)	BRACHYPELLIC (CM.)
<i>Inlet.</i> —			
Anteroposterior	12.0 to 13.0	11.5 to 12.25	10.5 to 11.5
Transverse	11.5 to 12.25	12.0 to 12.75	12.25 to 13.25
Posterior sagittal	4.5 to 5.5	4.25 to 5.0	4.0 to 4.5
<i>Midplane.</i> —			
Anteroposterior	12.0 to 13.0	11.75 to 13.0	11.5 to 12.75
Transverse	9.25 to 10.25	10.0 to 10.75	10.0 to 11.0
Posterior sagittal	4.75 to 5.5	4.5 to 5.5	4.5 to 5.5
<i>Outlet.</i> —			
Widest transverse (measured manually)	11.3	11.9	12.0

The incidence of the pelvic types studied in a larger group (1,100 women) was 19, 46, and 32 per cent, respectively.

In considering midplane constriction we are concerned with the relative shortening of two dimensions, the midplane transverse and the midplane anteroposterior diameters. In our experience shortening of one or both of these diameters is not uncommon and, when it exists, a knowledge of its extent is of considerable prognostic importance. When such contraction exists and the pelvic inlet diameters remain within average limits, the fetal head usually shows good engagement and labor proceeds normally until such a time as the head attempts to pass the midpelvic plane. It is at this level that the greatest difficulty in midforceps delivery is usually encountered.

In this study, as in the previous one, we have chosen to regard as the chief index to midplane contraction the shortened transverse or interspinous diameter and, for this purpose, we have designated all transverse diameters of less than 10 cm. as being evidence of midplane constriction. As in the previous series we have divided these *transversely* contracted midplanes into two groups: Group A (range 9.9 cm. to 9.6 cm.), Group B (range less than 9.6 cm.). We consider midplane *anteroposterior* shortening to be present in: dolichopellic-type pelves showing this diameter to be less than 12.00 cm.; mesatipellic-type pelves showing this diameter to be less than 11.75 cm.; brachypellic-type pelves showing this diameter to be less than 11.50 cm.

We feel that it is important to compare both old and new data for two reasons: first, because our added information substantiates our previous experience; and, second, our method of procedure in certain cases has undergone some change. The following data are self-explanatory:

	OLD SERIES	NEW SERIES	TOTAL
1. Number of pelves studied	153	167	320
2. Number of labors studied:			
1st	153	167	320
2nd	32	38	70
3rd	8	7	15
4th	1	0	1
3. Pelves showing midplane transverse less than 10 cm.	153	167	320
4. Group A (9.9 to 9.6 cm.)	65	83	148
Group B (9.5 cm. or less)	88	84	172
5. Group A, operative incidence:	36.3%	39.8%	37.8%
Low forceps	16	25	41
Midforceps	7	4	11
Cesarean sections	0	4	4
Group B, operative incidence:	55.8%	56.0%	55.9%
Low forceps	28	28	56
Midforceps	18	10	28
Cesarean sections	3	9	12
6. Pelves showing midplane transverse but no other shortening	73	104	177
Operative incidence	41.3%	45.2%	43.5%
Group B alone	45.2%	49.1%	-
7. Pelves showing midplane transverse shortening plus midplane anteroposterior shortening	75	40	115
Operative incidence	54.6%	52.5%	53.9%
Group B alone	65.0%	60.0%	63.5%
Types of Operation:			
Group A cases:	32	20	52
Low forceps	8	4	12
Midforceps	5	3	8
Cesarean sections	0	2	2
Group B cases:	43	20	63
Low forceps	15	5	20
Midforceps	10	2	12
Cesarean sections	3	5	8
8. Pelves showing midplane transverse plus midplane anteroposterior shortening:	75	40	115
Dolichopellic	27	14	41
Mesatipellic	36	24	60
Brachypellic	12	2	14
9. Pelves showing simple midplane transverse shortening:	153	167	320
Dolichopellic	65 (42.5%)	81 (48.6%)	146 (45.6%)
Mesatipellic	63 (41.2%)	68 (40.7%)	131 (41.0%)
Brachypellic	24 (15.7%)	16 (9.5%)	40 (12.5%)
Platypellic	1 (0.6%)	2 (1.2%)	3 (0.9%)
Subsequent Deliveries	32	38	70
Spontaneous, 1st delivery	16	17	33
Spontaneous, 2nd delivery	16	16	32
Operative, 2nd delivery	0	1	1
Operative, 1st delivery	16	21	37
Spontaneous, 2nd delivery	9	16	25
Operative, 2nd delivery	7	5	12

Comment

In surveying the two series we are impressed with the correlation of findings. The entire group (320 cases) shows a high percentage of operative deliveries associated with transverse midplane contraction: Group A, 37.8 per cent, and Group B, 55.9 per cent. When such contraction is associated with midplane anteroposterior shortening the operative deliveries rise to 63.5 per cent. The obvious conclusion is that, when midplane contraction is discovered, suitable measures must be considered for dealing with the situation. The in-

crease in cesarean sections from three in the first series (4.2 per cent of 72 operative deliveries) to thirteen in the second (16.3 per cent of 80 operative deliveries) shows that we are considering this type of delivery as preferable to difficult forceps deliveries and, by the same token, the decrease in midforceps in the second series is shown to be from twenty-five (34.7 per cent of 72 operative deliveries) to fourteen (17.5 per cent of 80 operative deliveries). The delivery by cesarean section of breech presentations at term with associated midplane contraction is the procedure of choice as far as we are concerned.

As in the previous series, the association of dolichopellic and mesatipellic types with relative midplane transverse constriction is of interest developmentally because of the apparent association of these forms with environmental conditions during the growth period, which has been discussed elsewhere.⁷ It should be remembered, however, that both of these types are also characterized by relatively increased anteroposterior room throughout the pelvis, so that adequate compensation is usually present.

It is interesting to consider the incidence of midplane contraction as it occurs in this clinic. In order to arrive at this figure we have studied the pelvic measurements in 1,009 consecutive primigravid patients. Of these, 350, or 34.7 per cent, revealed contraction according to our criteria in one or both midplane diameters. Two hundred eighty-seven of this 350 have been delivered of full-term infants on the teaching ward service of the hospital. One hundred sixty-seven of the 287 have shown midplane transverse contraction with or without anteroposterior shortening, whereas contraction of both anteroposterior and transverse diameters occurred in but forty instances.

Various formulary methods have been advocated for evaluating the adequacy of the midpelvis. Until further studies have resulted in more agreement on the subject, we prefer to continue using the simple criteria shown above, namely, classifying pelvis into two groups, A and B, dependent upon the degree of midplane transverse contraction with added consideration of the presence or absence of anteroposterior shortening. The adequacy of this method of evaluation may be seen in some measure by a fetal mortality of one in 167 cases (new series 0.6 per cent). There was no maternal mortality.

To recapitulate, when the midplane transverse diameter is less than 10.0 cm. without other midplane shortening, we may expect operative delivery in 43.5 per cent. When this shortening is combined with anteroposterior shortening, this incidence is 53.9 per cent, and when such transverse shortening becomes more marked, as in Group B, the incidence of this combination rises to 63.5 per cent.

Conclusions

1. Accumulated evidence from this and other studies shows that even moderate constriction at the midpelvis must be viewed with circumspection in every labor.
2. Such midplane constriction can only be discovered and measured accurately by roentgen techniques.
3. This being so, roentgen pelvimetry of every primigravida should become a routine procedure. In these days of periodic mass x-ray screening for other diagnostic purposes, it does not seem too much to ask that attention be directed to giving every woman in her first pregnancy the benefits of pelvic roentgenometry. It should be pointed out that one such examination in a woman's lifetime is usually sufficient.

We wish to record appreciation of the assistance of Miss Mary L. Shea, R.N., in the preparation of this paper.

References

1. Thoms, H., and Schumacher, P. C.: *AM. J. OBST. & GYNEC.* 48: 52, 1944.
2. Hanson, S.: *Surg., Gynec. & Obst.* 59: 102, 1934; *AM. J. OBST. & GYNEC.* 35: 228, 1938.
3. Mengert, W. F.: *J. A. M. A.* 138: 169, 1948.
4. Groskloss, H. H., Robbins, O. F., and Moehn, J. T.: *AM. J. OBST. & GYNEC.* 56: 1090, 1948.
5. Thoms, H., and Wilson, H. M.: *Yale J. Biol. & Med.* 13: 6, 1941.
6. Thoms, H.: *AM. J. OBST. & GYNEC.* 42: 957, 1941.
7. Thoms, H.: *AM. J. OBST. & GYNEC.* 54: 62, 1947.

Day, Lois A., Hall, Byron E., and Pease, Gertrude L.: **Macrocytic Anemia of Pregnancy Refractory to Vitamin B₁₂ Therapy; Response to Treatment With Folic Acid: Report of Case**, *Proc. Staff Meet., Mayo Clin.* 24: 149, 1949.

In the case reported, the patient developed anemia during the seventh month of her second pregnancy; nausea, vomiting and diarrhea, and soreness of the mouth and gums occurred and within a week she showed marked weakness, extreme pallor, swelling of the legs and feet and puffiness of the face. Blood studies showed macrocytic anemia; bone-marrow biopsy showed hyperblastic marrow with megaloblastic erythropoiesis and active myelopoiesis. The parenteral administration of liver extract and of vitamin B₁₂ failed to elicit a hematopoietic response. The patient's clinical condition became worse after B₁₂ had been given. The parenteral administration of pteroylglutamic (folic) acid caused an immediate hematopoietic response with a reticulocyte peak on the sixth day. The clinical improvement was also rapid, and at the end of two weeks of folic acid therapy, the patient felt entirely well. She had a normal delivery and puerperium. The administration of folic acid (15 mg. weekly) was continued for six weeks after the patient's discharge from the hospital, as macrocytic anemia has been known to recur during this period. Examination of the bone marrow of the infant approximately an hour after birth showed normoblastic erythropoiesis.

In a review of the literature it was found that the "dramatic" response of the macrocytic anemia of pregnancy to folic acid therapy has been reported by others. One case has been reported by Bethel, in which the administration of vitamin B₁₂ parenterally for ten days failed to produce any hematopoietic response, but the subsequent administration of folic acid (given by mouth, 10 mg. daily) resulted in a prompt hematopoietic response and clinical improvement, as in the author's case. These findings indicate that a deficiency of pteroylglutamic (folic) acid is responsible for the macrocytic anemia of pregnancy. In the authors' case, it is noted that, five days before delivery, the urinary excretion of 17-ketosteroids and of estrogen was below normal for the ninth month of pregnancy, while the urinary chorionic gonadotropins were at a high normal level.

HARVEY B. MATTHEWS.

INTRAVENOUS ALCOHOL DURING LABOR*

STANTON BELINKOFF, M.D., AND ORRIN W. HALL, JR., M.D.,† NEW BEDFORD, MASS.

(From the Department of Anesthesia, St. Luke's Hospital)

THE search for an ideal means of relieving the pain during childbirth is continuing at an unabated rate. Thus far many procedures have been recommended, but none fulfills all the safety requirements for both mother and child when used in efficacious doses. Various combinations of morphine, scopolamine, Nembutal, Demerol, paraldehyde, and rectal ether, and more recently continuous caudal and saddle block, have all been tried with varied success. This paper is being presented to record our experiences with the intravenous administration of alcohol.

The use of intravenous alcohol is not new. Good results have been obtained in the relief of postoperative pain.¹⁻⁴ The patient reaches the stage of euphoria where, even though he admits the presence of the pain, he still says it doesn't bother him. This corresponds to the stage in oral ingestion referred to colloquially as "feeling no pain." One of us (S. B.) has had personal experience with the parenteral method following a major abdominal procedure and the relief of postoperative pain and the feeling of well-being and euphoria were very welcome.

In addition to its pain relief, alcohol has several other good features. It is a food of high carbohydrate value which is completely utilized in the body. This added nourishment is beneficial for patients who are otherwise not taking food.⁵ The solvent helps maintain the fluid balance.

Procedure

One of the antecubital veins was usually selected for the administration, with the arm securely fastened to an armboard. An 18 gauge needle was used so that a rapid flow could be obtained when necessary. The patients were instructed not to move their arms and were checked from time to time to see if there was any extravasation. It was feared that the 5 per cent alcohol might cause a slough if it found its way into the subcutaneous tissues. These fears have been unjustified thus far for in two instances large subcutaneous infiltrations were noted with no deleterious effects. This should not be taken to mean that sloughs may not occur in other patients if similar circumstances should arise.

Now that the solution is available in water as well as saline, there is no limit on the amount that can be given. At first when only saline was available an arbitrary limit of 1,000 c.c. was set. At present the first bottle used is the alcohol in saline and subsequent bottles, if needed, are alcohol in water.

The cases being presented were taken from the ward service in a more or less haphazard fashion. The only criterion for their selection was that one of us was available to see and examine the patient and start the alcohol at the proper time. An effort was made to eliminate toxic cases from consideration since it was felt that those with eclampsia or pre-eclampsia already had some liver disturbance and the added task of detoxifying and using the alcohol might be too

*The alcohol used in this study was a commercial preparation made by the Abbott Laboratories and graciously supplied to us by them.

†Present address, University of Pennsylvania Hospital, Philadelphia, Pa.

TABLE I

NO.	PATIENT	AGE	PARA	CM. DILA- TION CER- VIX	FRE- QUENCY OF PAINS (MIN- UTES)	AMT. ALCOHOL (C.C.)	STARTED AT	ENDED AT	DELIVERY AT	TYPE DELIVERY	ANES- THESIA FOR DELIVERY	PERINEUM
1	P. D.	28	2	3	5	700	8:15	8:45	8:45	Spont.	None	Intact
2	A. D.	26	1	2	5	1,000	7:45	12:30	2:30	Spont.	None	Intact
3	A. B.	30	3	2	5	800	11:30	3:30	3:30	Spont.	None	Intact
4	E. M.	26	1	3	5	1,500	1:15	7:00	10:40	Spont.	GOE	Intact
5	E. G.	24	1	4	5	500	10:30	12:00	12:00	Spont.	GO	Intact
6	R. S.	35	5	3	5	500	10:00	12:00	1:30	Spont.	None	Intact
7	A. P.	31	8	4	5	750	3:30	5:00	10:00	Spont.	None	Intact
8	T. S.	20	0	3	3	1,000	2:00	6:15	6:45	Spont.	Ether	Intact
9	M. S.	31	4	3	3	350	10:00	11:15	11:15	Spont.	None	Intact
10	I. C.	22	2	2	4	1,000	10:30	12:00	3:50	Spont.	Ether	Intact
11	G. D.	31	1	4	4	500	1:30	2:00	2:00	Spont.	Ether	1° lac.
12	A. H.	23	0	2	5	1,000	11:00	2:30	10:30	Spont.	GOE	M. E.
13	A. L.	25	2	4	4	1,000	11:00	4:15	8:00	Spont.	GOE	Intact
14	M. J.	16	0	3	5	1,000	4:30	10:00	2:40	L. F.	GOE	M. E.
15	A. J.	23	1	3	8	1,000	2:00	4:20	4:30	L. F.	GOE	M. E.
16	F. W.	21	0	5	4	1,200	5:00	7:15	7:15	Manual rot.	Spinal	M. E.
17	M. H.	23	1	3	5	1,000	11:45	1:30	1:35	L. F.	Ether	Intact
18	P. M.	32	0	2	3	1,500	10:00	4:00	4:30	L. F.	GOE	M. E.
19	C. S.	29	2	4	5	700	3:00	4:15	4:15	Spont.	None	Intact
20	E. W.	24	1	3	5	1,000	6:00	9:30	10:30	Spont.	None	Intact
												Demerol, 50 mg.
												Demerol, 100 mg., scopolamine 1/200 grain
												Demerol, 100 mg.
												Stillborn
												Demerol, 100 mg., scopolamine 1/200 grain

much of a burden. Although this is only a theoretical consideration, still we felt obliged to assume no unnecessary risks. However, none were eliminated for toxic symptoms. These twenty cases presented in Table I were taken in order of admission, the only exceptions to their consecutive order being when neither one of us was available.

The basic technique of administration of the alcohol was 200 c.c. in less than fifteen minutes to initiate the blood level followed by a constant drip of 100 drops per minute. The body can metabolize about 10 c.c. of the alcohol in an hour, completely oxidizing it. Therefore, using a 5 per cent solution up to 200 c.c. per hour can be given without increasing the blood level. However, all cases were individualized to compensate for varying severity of pain and speed of labor.

Blood level determinations were done to evaluate how much would be needed to produce the necessary state of euphoria.

The official Navy test described in the laboratory manual of the Naval Medical School was used, where the blood sample is heated to volatilize the alcohol it contains and the alcohol vapor is then drawn into the reagent by a suction pump. The color change is produced by the quantitative reduction of potassium dichromate by alcohol in the presence of sulfuric acid. Colorimetric readings are then done against standards prepared for this purpose, or else with a photoelectric apparatus. Both of these methods were used with insignificant variations between them.

With this method normal blood may show a minimal change often comparable to the 0.5 mg. standard. Such changes are disregarded and considered negative. The average drunken individual will be found to have between 2.0 and 3.0 mg. per c.c. of blood. The incidence of coma increases from 3.5 to 5.0 mg. where all are comatose and perhaps fatally so. Clinical deaths have occurred with concentrations of 4.5 to 5.0 mg. per c.c.

Results

Alcohol blood-level determinations proved very interesting. It was found that a significant level was obtained about fifteen to twenty-five minutes after administration was begun. When the level was maintained at from 1.2 to 1.8 mg. per c.c. the patient felt fairly comfortable and did not mind her pains. In several instances where the alcohol was inadvertently administered in large quantities in a short period of time, the patient was nauseated and vomited. A level done on one of these patients was 2.9 mg. per c.c., a value usually found with the drunken state. Satisfactory euphoria and analgesia were produced with a blood level well below that usually considered to be drunkenness.

Studies done on the cord blood immediately following delivery showed a level slightly below that of the maternal blood, usually about 20 per cent less. The placenta seemed to act as a slight barrier to the passage of the alcohol from the mother's blood stream to that of the baby. This blood level in our cases was not high enough to produce any change in the baby or to interfere with the spontaneous initiation of respirations.

Good analgesia was obtained in 80 per cent of the cases, no other sedation being necessary. Some of the patients, however, objected to the fact that they knew everything that was going on in contrast to previous deliveries where amnesia had been produced.

Discussion

As can be seen from Table I the amount of alcohol given to the patients varied greatly, from a minimum of 350 c.c. to a maximum of 1,500. Only four of the twenty patients required any additional sedation to ease the pains of their labor. The other sixteen were able to stand the pains until the time of delivery

and seven of them, all multiparas, were delivered without any anesthesia. Those requiring episiotomies or forceps were given spinal or some form of inhalation anesthesia.

There was no morbidity or mortality among the mothers. There was one stillborn infant. The mother was a primipara who received 1,000 c.c. of alcohol too early in her labor with the result that the contractions apparently stopped and the patient went to sleep. Two hours after the conclusion of the alcohol infusion, the pains started again eight minutes apart and the cervix was 2 cm. dilated. Three hours later the cervix was 3 cm. dilated, and the blood pressure, pulse, and fetal heartbeat were all within normal limits. Eight hours after the end of the alcohol infusion the patient delivered spontaneously a stillborn in the right occipitoanterior position under gas-oxygen-ether anesthesia, with a midline episiotomy. An autopsy was obtained which showed nothing. The fetal heart was in good condition one hour before delivery. The patient had no sedation other than the alcohol. The only reason for the stillborn is possibly that the cord was compressed by either the presenting part or the shoulder. In our minds the alcohol had no effect.

In some instances the patients when questioned would say yes they were having contractions but that they did not mind them. Some of them would state that they felt drunk but none of the patients knew what was being given to them except that it was something that would help their pains.

It was noted that if the alcohol was started before the patient was in good labor and the cervix 2.5 to 3 cm. effaced, the progress of labor was markedly slowed down or stopped. If, however, it was started when the patient was 3.5 to 4 cm. dilated, it seemed to accelerate the progress of labor. Therefore, an accurate gauge of the patient's status must be made before the administration of the alcohol is started.

There was a marked individual variation in the response to the same dose. Some patients required much more than others to achieve the same euphoria.

With the exception of the one instance of stillbirth, all the babies cried immediately and spontaneously, some even before the delivery of the whole body. This was in contrast to the resuscitative measures required for many of the infants born of mothers who have had Nembutal and scopolamine.

A marked feature of the sedation with alcohol was that all of the patients lay quietly in bed. None of them presented the irrational and delirious state often seen with the methods of analgesia in which the production of amnesia is a desired factor. In these patients, although no amnesia was obtained, and they all remembered having gone through the labor, in most instances they said they did not mind it.

In order to obtain good results with this agent, close supervision of the patient must be maintained. The rate of flow must be regulated according to the response of the patient. This requires constant attendance which is not always possible in the overcrowded, somewhat understaffed hospital which is the rule today.

Conclusion

The administration of intravenous alcohol in our hands has not proved to be the ideal method for the relief of the pain of childbirth. In many cases, however, if its administration is closely supervised, an excellent result can be obtained.

References

1. Craddock, F. H., Jr., and Craddock, F. H., Sr.: *J. M. A. Alabama* 12: 134, 1942.
2. Moore, D. C., and Karp, M.: *Surg., Gynec. & Obst.* 80: 523, 1945.
3. Behan, R. J.: *Am. J. Surg.* 69: 227, 1945.
4. Rennann, E. T.: *J. Tennessee M. A.* 39: 207, 1946.
5. Rice, C. O., Strickler, J. H., Orr, B., and Sanderson, D.: *Journal Lancet* 68: 91, 1948.

CEROID PIGMENT IN THE HUMAN OVARY

JAMES W. REAGAN, M.D., CLEVELAND, OHIO

*(From the Institute of Pathology, Western Reserve University and
University Hospitals of Cleveland)*

GYÖRGY and Goldblatt¹ employing frozen sections observed a light yellow or greenish-yellow globular material in the periportal fibrous connective tissue of rats with experimental dietary injury of the liver. These globules did not contain iron, were insoluble in organic fat solvents, and gave a positive oxidase stain in frozen sections. Since the globules reacted as lipids in paraffin and frozen sections, and were insoluble in lipid solvents, they were thought to be lipoidal material in combination with protein and presumably derived from necrotic hepatic cells. Edwards and White² also identified a "canary" yellow pigment in the livers of rats fed with P-dimethylaminoazobenzene and considered it to be a lipoidal substance in conjugated form, suggesting in a later paper³ that it was derived from disintegrating hepatic tissue. Lillie, Ashburn, Sebrell, Daft, and Lowry⁴ offered the name "ceroid" (waxlike) for this globular material which they found in the liver, lungs, spleen, lymph nodes, bone marrow, and adrenal cortex of the rat in experimental dietary cirrhosis. The pigment has also been identified in the ovaries and testes of the rat in avitaminosis E by Mason and Emmel,⁵ and Pappenheimer and Victor⁶ demonstrated an acid-fast pigment, presumably ceroid, in many sites in man.

Material

The purpose of this investigation is to study the distribution and character of a similar pigment in the human ovary. For this purpose fifty ovaries were selected at random from the surgical specimens submitted to the Institute of Pathology of the University Hospitals and Western Reserve University. Numerous special stains were employed as will be indicated.

Macrophages containing a pale yellow or pale brownish-yellow pigment are present in hematoxylin-eosin preparations of forty-four ovaries in this series. They exist bilaterally in four instances in which both ovaries were available for study. While they are more common at the periphery of the corpus luteum in regression, in the connective tissue ingrowth of the theca interna, about the follicle in atresia, or within the interstitial connective tissue where they lie in a perivascular location, they also occur within the substance of the corpus luteum and rarely in endothelial-lined spaces. The youngest age at which the pigment exists is 19 years and the oldest is 55 years. Six of the ovaries studied by multiple but not serial sections did not contain the pigment. Two of these are from patients aged 15 and 16 years in which the menarche is not apparent, two are from patients aged 25 and 42 years, and two are from patients in the climacterium aged 62 and 64 years. The limited size of this series and the inadequate age distribution do not permit accurate deductions as to the occurrence of the pigment; however, it is common during the active sexual period of life and is not present in several fetal ovaries examined.

The macrophages containing pigment average 30 microns in greatest diameter but vary from 8 to 40 microns in diameter. The spherical nucleus with compact deeply basophilic nuclear chromatin averages 6 microns in diameter and is usually situated centrally in the cell. Occasionally the nucleus is eccentric

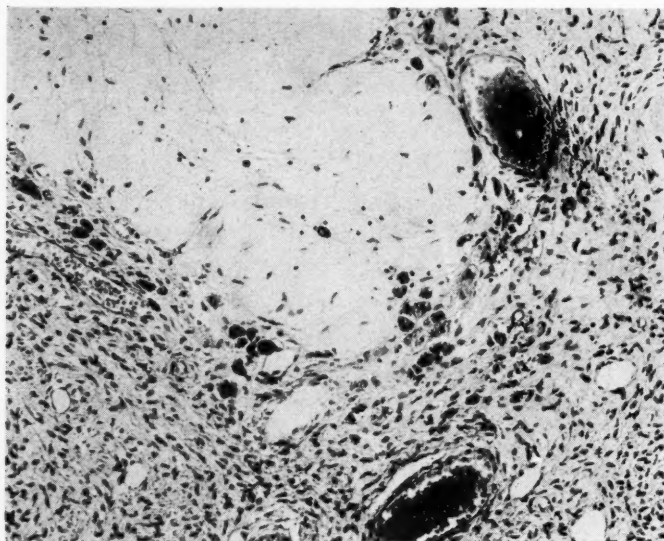


Fig. 1.—Macrophages containing ceroid pigment situated at the periphery of an involuting corpus luteum. Mallory's hemofuscin stain. ($\times 142$.)

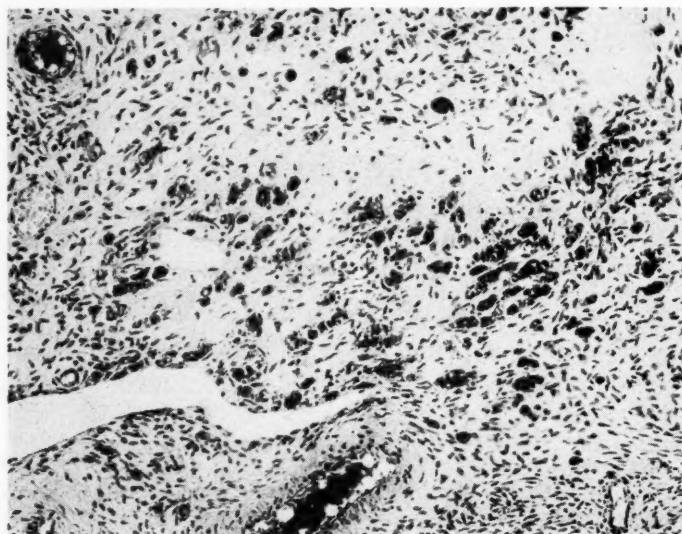


Fig. 2.—Macrophages containing ceroid pigment located in the interstitial tissues in a perivascular distribution. Mallory's hemofuscin stain. ($\times 142$.)

in position and two nuclei may exist in the cell. Many of the cells are vacuolated and irregular in outline with pigment accumulations of variable size, while uniform pigment globules occur in cells with a regular outline.

The pigment is pale yellow or pale brownish-yellow in hematoxylin-eosin preparations, acid fast with the Ziehl-Neelsen technique, and does not contain iron with Perles' reaction. In paraffin sections it stains with methyl green,

with Sudan IV, and is oxidase positive. The pigment reduces silver and Turnbull's blue is not formed with Schmorl's ferric chloride potassium ferriyanide reagent. With Mallory's hemofuscin method the pigment stains red. These staining reactions are similar to those of ceroid as reported by Endicott and Lillie⁷ on the pigment of dietary cirrhosis in rats.

Ragins and Popper⁸ have previously noted the similarity of ceroid to the "wear and tear" pigment of the human atretic follicle under the fluorescent microscope, and accordingly several sections from this series were submitted to Dr. Popper for examination. He states that the more lightly staining pigment reveals a marked fluorescence with a brownish hue when the filter system is employed, although the fluorescence is not as bright as in ceroid of livers with experimental cirrhosis or in frozen sections of ovary which he examined many years ago but he agrees that the pigment is ceroid.

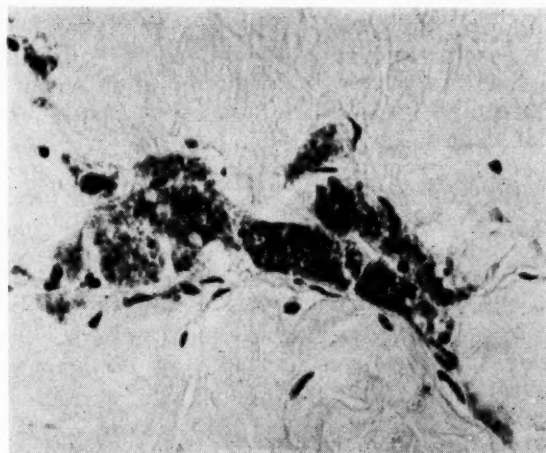


Fig. 3.—Macrophages containing ceroid pigment located within the substance of an involuting corpus luteum. Note the vacuolization of several of the cells. Mallory's hemofuscin stain. ($\times 507$.)

Discussion

A variable number of macrophages containing a pale yellow or pale brownish-yellow pigment are commonly associated with the corpus luteum of the human ovary. These are not related to the mature corpus luteum but appear during the stage of regression to remain at the periphery of the involuting corpus luteum for varying periods of time. They are less frequently associated with the corpus albicans especially when hyalinization is advanced. The pigment may also be deposited in the interstitial tissues of the ovary in the region of follicular cysts and may occur in perivascular sites. In one instance phagocytes were present both within and beneath the epithelium of a serous cystadenoma of the ovary.

Where associated with the corpus luteum the pigment usually appears first in a finely granular form deposited irregularly in the outer third of the luteinized zone, and may outline the vacuoles of macrophages in this location. As regression progresses, larger and more deeply staining pigment globules occur within macrophages at the periphery of the involuting corpus luteum. The macrophages are variable in number and somewhat irregular in distribution, although they frequently occur in aggregates situated in sites comparable to the pre-existing paralutein cells. Because of the difficulty in estimating the exact age of the atretic corpus luteum histologically and the individual variations in atresia, it is not possible to determine accurately the age at which the pigment is formed

nor is it possible to state that all corpora lutea of a comparable age contain this pigment in the same degree. The evidence available suggests that the pigment is not always present in involution although we offer no explanation for this.

During the later phases of regression the macrophages in relation to the corpus luteum are few in number and occur more commonly in perivascular sites. This suggests a migration of the cells because of the caliber of the vessels and their location deep in the substance of the ovary. The lymphatics may also play a part in removing the pigment since the cells are present in large thin-walled endothelial-lined spaces.

Ever since the time of its recognition in experimental hepatic cirrhosis, the chemical nature and mode of production of ceroid have presented a complex problem. Blumberg and Grady⁹ thought the material was hemofuscin; however, Edwards and White² and Endicott and Lillie⁷ were able to differentiate ceroid from hemofuscin on the basis of staining reactions, location, and appearance. Popper, György, and Goldblatt¹⁰ regarded the material as a lipid in conjugation with a protein similar to the "wear and tear" pigments. In 1944 Endicott¹¹ was able to produce ceroid experimentally in rats by subcutaneous injection of oils, and suggested that the reaction may be an oxidation of the fatty acids at the double bonds with the formation of unstable peroxides which are subsequently polymerized. The latter concept is also supported by Mason, Dam, and Granados.¹² The production of ovarian ceroid has been investigated by Brenner.¹³ He suggests that the breakdown of carotene and vitamin A is catalized by an enzyme lipoxidase resulting in the formation of peroxides of fatty acids which subsequently undergo polymerization to form ceroid. This concept is favored by the fact that the fluorescence of vitamin A diminishes as the process of involution of the corpus luteum progresses and conversely ceroid undergoes concentration according to Ragins and Popper, and the almost constant relationship of the pigment to the regressing corpus luteum histologically suggests origin in the disintegration of the lutein cells.

Summary

In the human ovary a pale yellow globular pigment occurs within macrophages at the periphery of the involuting corpus luteum and in the interstitial tissues. The pigment, ceroid, is probably a disintegration product of lutein cells.

References

1. György, P., and Goldblatt, H.: *J. Exper. Med.* **75**: 355, 1942.
2. Edwards, J. E., and White, J.: *J. Nat. Cancer Inst.* **1**: 157, 1941.
3. White, J., and Edwards, J. E.: *J. Nat. Cancer Inst.* **3**: 43, 1942.
4. Lillie, R. D., Ashburn, L. L., Sebrell, W. H., Daft, F. S., and Lowry, J. V.: *Pub. Health Rep.* **57**: 502, 1942.
5. Mason, K. E., and Emmel, A. F.: *Yale J. Biol. & Med.* **17**: 189, 1944.
6. Pappenheimer, A. M., and Victor, J.: *Am. J. Path.* **22**: 395, 1946.
7. Endicott, K. M., and Lillie, R. D.: *Am. J. Path.* **20**: 149, 1944.
8. Ragins, A. B., and Popper, H.: *Arch. Path.* **34**: 647, 1942.
9. Blumberg, H., and Grady, H. G.: *Arch. Path.* **34**: 1035, 1942.
10. Popper, H., György, P., and Goldblatt, H.: *Arch. Path.* **37**: 161, 1944.
11. Endicott, K. M.: *Arch. Path.* **37**: 49, 1944.
12. Mason, K. E., Dam, H., and Granados, H.: *Anat. Rec.* **94**: 265, 1946.
13. Brenner, S.: *South African J. M. Sc.* **11**: 173, 1946.

CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS*

A Report of 2,015 Consecutive Cases

HARRY A. LUSK, M.D., GLENDALE, CALIF.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital,
Ann Arbor, Mich.)

THE historical background of continuous caudal analgesia has been recorded in many papers and will not be repeated here. We have used the Hingson-Edwards continuous caudal technique in our clinic since January, 1943. In this series we used caudal analgesia in 2,015 pregnant women, of which number 1,989 were given the procedure for delivery. It was given in twenty-six cases for gynecologic reasons such as dilatation and curettage of incomplete abortions (Table I). In this same period we had 3,157 deliveries on the maternity service, using caudal on only 63 per cent of the patients (Table II). However, as our experience with the method increased, so did our use of it.

TABLE I. ANALYSIS OF CAUDAL SERIES

Obstetrical caudals	1,989
Gynecologic caudals (D. & C.—incomplete abortions)	26
Total caudals in series	2,015

TABLE II. INCIDENCE OF CAUDAL IN PERIOD OF STUDY

Number of deliveries during period of study	3,157
Number of obstetrical caudals given during period	1,989
Incidence	63.0%

Method

The technique used was described in 1942.^{1, 2, 3} A 19 gauge, malleable steel needle was introduced into the caudal canal under aseptic conditions; proper checks were made to avoid subdural or intravenous injection; and an analgesic agent—usually 1.5 per cent Metycaine was then intermittently injected through a closed system. The analgesia was started when the patient was in good labor and the cervix was dilated to 4 cm. in primiparas, 3 cm. in multiparas. Checks of the blood pressure and fetal heartbeat were made routinely at the times of injection and oftener if indicated. For mild blood pressure drops we did no more than to raise the feet; but for systolic pressures of 80 mm. Hg, or below, suitable vasopressor medication was used. When the patient was turned on her back in the delivery room, the systolic pressure and fetal heartbeat were again checked, and if the pressure fell it could be restored by temporarily returning the patient to her lateral position. We have in a few instances used the repeated single injection technique reported by Hanley and Malone,⁴ and Brown⁵; and in a few instances the catheter method reported by Irving,⁶ but we prefer the technique just described.

Good obstetric analgesia should be reliable, flexible, and relatively non-toxic to the patient or the child. A completely successful caudal is not supplemented by any other agent during the delivery, and the patient remains calm, conscious, and cooperative throughout. In our series, 1,583 (77.6 per cent) had complete relief. Two-hundred thirty-one (11.62 per cent) were partial failures and required supplementary anesthesia for the delivery. One hundred twenty-eight (6.44 per cent) were attempted, satisfactory caudal analgesia was not obtained, and the caudal attempt was abandoned. Eighty-seven (4.37 per cent) were discontinued, after having been established (Table III).

TABLE III. RELIABILITY OF CAUDAL ANALGESIA

Completely satisfactory caudals	1,543	77.60%
Those needing supplementary anesthesia	231	11.62%
Caudal attempted, anesthetic induction failures	128	6.44%
Caudals discontinued	87	4.37%
Total caudals	1,989	100.00%

Of the 128 unsuccessful attempts to establish caudal analgesia, bony abnormalities were thought to account for fifty-seven (44.5 per cent) of the failures (Table IV). We had also sixteen spinal taps, and eleven bloody taps which gave us failures. Obesity accounted for eight (6.25 per cent) of these failures, and another eight cases had no anesthesia in spite of apparently satisfactory physical checks. Twenty-eight (21.85 per cent) of the unsuccessful attempts were attributed to a miscellany of reasons: in three cases the uterine contractions stopped with the initial dose; in five cases marked "technical failures," the failure was in the equipment to carry on continuous caudal, not in the patient; in six instances caudal was started too late for relief; and in two cases in which the patients were quite short, analgesia was unilateral. We had severe toxic reactions in three cases, one severe dizziness, and two of syncope. A caudal was attempted and abandoned in two cases where previous pilonidal surgery had been done, although we have been able to establish entirely satisfactory anesthesia in other patients who have had pilonidal cysts removed. Five patients became personality problems with the caudal. And in two cases, where previous caudal had been satisfactory, a satisfactory caudal could not be obtained, raising the question of refractoriness of the patient to repeat caudals.

TABLE IV. ANESTHETIC INDUCTION FAILURES

Total starting failures		128	100.00%
Bony Abnormalities		57	44.50%
a. Hiatus defects	36		
b. Open sacrum	21		
Spinal taps		16	12.50%
Bloody taps		11	8.60%
Obesity		8	6.25%
No anesthetic level		8	6.25%
Miscellaneous		28	21.85%
a. Contractions stopped	3		
b. Technical failures	5		
c. To late for relief	6		
d. Unilateral analgesia, patient short	2		
e. Severe dizziness	1		
f. Syncope	2		
g. Old pilonidal surgery	2		
h. Personality (patient reacted to caudal with a variety of functional complaints)	5		
i. Second caudal—question of refractory patient	2		

Eighty-seven (4.37 per cent) caudals were discontinued after apparently successful starts (Table V). These caudals had been running for an average of five hours, fifty-five minutes. Forty-eight (55.2 per cent) were discontinued for lack of progress in labor. Twenty (23.2 per cent) showed a progressively decreasing level of anesthesia. Five showed a recurrent tendency for toxic effects, and three more were associated with significant, recurrent blood-pressure drops. One patient (D. M.) developed a spinal effect after her second injection; and in one patient the needle was displaced. Nine caudals were discontinued electively in preparation for a delivery where the operator thought it would be best for the patient to be asleep, as in delivery of a monster, or where difficult forceps rotation was anticipated and greater general relaxation was desired.

TABLE V. CAUDALS DISCONTINUED

Average duration	5 hours 55 minutes	
Number discontinued	87	100.00%
Lack of progress of labor	48	55.20%
Decreasing level of anesthesia	20	23.20%
Preparation for other obstetric procedures—see text	9	10.32%
Recurrent toxic symptoms	5	5.74%
Recurrent blood pressure drop	3	2.90%
Spinal effect	1	1.15%
Displaced needle	1	1.15%

Some evidence of toxicity was noticed in 187 (9.4 per cent) cases (Table VI). A pronounced blood-pressure drop was the most common symptom. One hundred twenty-six patients (6.32 per cent) had a moderately severe fall, and thirty-two (1.61 per cent) had a severe fall to less than 80 mm. systolic pressure. One patient (F. D.) suffered a systolic pressure drop to 40 mm. This persisted despite treatment. However, the fetal heart remained strong, and the patient was delivered of a healthy baby who required no resuscitation.

TABLE VI. TOXIC EFFECTS

Total caudals	1,989	100.00%
Blood Pressure Fall		
a. To 80 mm. Hg	126	6.32%
b. Less than 80 mm.	32	1.61%
Nausea and vomiting	21	1.05%
Ptosis left eyelid	3	0.15%
Syncope	2	0.10%
Headache	2	0.10%
Spinal effect	1	0.05%
Deaths	0	
Total toxic effects	187	9.40%

We found moderate nausea and vomiting in twenty-one patients (1.05 per cent). A majority of patients will have an occasional emesis during labor, even without caudal, so occasional vomiting did not cause us much concern.

We had three interesting cases in which the patient had ptosis of the left eyelid. This would correct itself if the patient were turned to the right side, but would recur when she was returned to her left side. There was no permanent effect.

In this series we have had but one infection at the caudal site. We have had three cases of postpartum urinary retention which may have been due to caudal. We have had no known paresthesias, but we have tried to avoid caudal analgesia in patients with a history of functional complaints.

In this series the average time from first to the last injection was three hours, forty-six minutes (Table VII). The patients received an average dose of 111.25 c.c. of 1.5 per cent Metycaine. The average estimated blood loss was 262 c.c. We used caudal analgesia on all types of cases, and include in this series forty-two cesarean sections, twenty-eight (66.7 per cent) of which have been entirely successful.

TABLE VII. AVERAGE CAUDAL FIGURES

Average time, first to last injection	3 hours, 46 minutes
Average No. of c.c. 1.5 per cent Metycaine injected	111.2 c.c.
Average estimated blood loss	262.0 c.c.

A criticism of caudal analgesia is that it increases the number of forceps deliveries and the number of occipitoposterior presentations. A review of 1,106 cases delivered at the University Hospital prior to the use of caudal was made to give us a control group (Table VIII). The common analgesics in the control group were barbiturates and scopolamine. Nitrous oxide, oxygen, and ether as indicated were the principal anesthetics. There were 65.5 per cent operative obstetrical deliveries in our caudal series as compared to 25.7 per cent in the precaudal controls. With caudal our outlet forceps incidence has increased to 41.2 per cent. Our use of outlet forceps consists of little more than lifting the head over the perineum, thus saving time for the mother and attending physician, and is not traumatic to either mother or child. Our low forceps incidence is nearly the same in the caudal, 23.3 per cent, as in the pre-caudal group, 23.7 per cent. The number of midforceps deliveries has decreased with caudal from 1.45 per cent to 0.95 per cent and we have had no high forceps deliveries under caudal. Although there has been a considerable increase in the incidence of forceps deliveries, it should be remembered that in recent years there has been a rather general change of philosophy toward a high frequency of outlet or "prophylactic" forceps. Thus, the anesthetic agent is not the only factor of importance.

TABLE VIII. FORCEPS DELIVERIES, CAUDAL AND CONTROL* GROUPS

	CONTROL		CAUDAL GROUP	
	NO.	PER CENT	NO.	PER CENT
Number of deliveries	1,106	100.0	1,989	100.0
Outlet forceps	00	00	819	41.2
Low forceps	263	23.7	463	23.3
Midforceps	15	1.45	19	0.95
High forceps	1		0	--
Total forceps	279	25.2	1,301	65.4
Versions and extractions	6	0.5	2	0.1
Operative deliveries	285	25.7	1,303	65.5

*Control Group, deliveries, June, 1940, to June, 1942, no caudal.

The increased number of occipitoposterior positions with the use of caudal has been mentioned by Hanley and Malone,⁴ Nicodemus,⁷ and Irving.⁶ Irving reported an increase in Scanzoni rotations in his series from 4.3 per cent to 7.3 per cent. According to our interpretation of Nicodemus' report, this author noted an incidence of 18.8 per cent posterior presentations in his 500 precaudal patients, and 24.4 per cent in 500 patients treated with caudal. In our control group of 1,106 we found 1.3 per cent requiring manual or forceps rotation, whereas in our caudal series 7.4 per cent required rotation or were delivered as persistent occiput posterior (Table IX). In our series we have noted a fivefold increase in the number of unrotated posterior presentations at the time of delivery.

TABLE IX. INCIDENCE OCCIPITOPOSTERIOR PRESENTATION AT TIME OF DELIVERY

	CONTROL		CAUDAL GROUP	
	NO.	PER CENT	NO.	PER CENT
Total number cases	1,106	100.00	1,989	100.00
Manual rotation	7	1.26	23	1.16
Forceps rotation	7		114	5.74
Persistent occiput posterior	--		10	0.53
Total	14	1.26	147	7.40

An important feature of caudal analgesia is the safety of the infant. This has been shown by Hingson and his co-workers.⁸ In his "Philadelphia" series he shows a stillbirth rate per thousand live births for "caudal . . . 9.1; control . . . 24.8" In the "Memphis" series he gives the stillbirth rate per thousand live births, for different anesthetics, as "caudal . . . 18.4; spinal . . . 45.2; general . . . 56.3; none . . . 63.6" In our precaudal series there were 32 stillbirths in 1,106 deliveries, a rate of 30.1 stillbirths per thousand live births. In our caudal series we had 21 stillbirths giving us a rate of 10.67 stillbirths per thousand live births (Table X). This compares favorably with the Philadelphia study.

TABLE X. STILLBIRTHS AND CAUDAL ANALGESIA

	BIRTHS	STILLBIRTHS	RATE PER THOUSAND
Control*	1,106	32	30.1
Caudal	1,989	21	10.67

*Control Group, 1,106 precaudal deliveries.

Summary

We have presented a series of 2,015 caudal analgesias, of which 1,989 have been for delivery. In our hands there is a 77.6 per cent reliability. There was an increase in incidence of forceps deliveries, from 25.2 per cent to 65.4 per cent, but actually this is of no great significance, for the increase has been in prophylactic or outlet forceps. There is a fivefold increase in occipitoposterior presentations at the time of delivery. In this series we had no deaths, only three moderately serious toxic reactions, and no serious postpartum complication. There has been a reduction in the stillbirth rate per thousand live births which compares favorably with Hingson's Philadelphia findings.

Conclusion

Caudal analgesia is not a panacea, but in careful hands it offers a good method of pain relief during labor and delivery, and properly used appears to be safe for mother and child.

References

1. Lull, C. B., and Hingson, R. A.: Control of Pain in Childbirth, Philadelphia, 1944, J. B. Lippincott Company.
2. Edwards, W. B., and Hingson, R. A.: *Am. J. Surg.* **57**: 459-464, 1942.
3. Hingson, R. A., and Edwards, W. B.: *Anesth. & Analg.* **21**: 301-311, 1942.
4. Hanley, B. J., and Malone, C. M.: *AM. J. OBST. & GYNEC.* **50**: 306-311, 1945.
5. Brown, W. E.: *AM. J. OBST. & GYNEC.* **55**: 717-723, 1948.
6. Irving, F. R., Lippincott, C. A., and Meyer, F. C.: *New York State J. Med.* **43**: 1023-1029, 1943.
7. Nicodemus, R. E., Ritmiller, L. F., and Ledden, L. J.: *AM. J. OBST. & GYNEC.* **50**: 312-318, 1945.
8. Hingson, R. A., Edwards, W. B., Lull, C. B., Whitacre, F. E., and Francklin, H. C.: *J. A. M. A.* **136**: 221-229, 1948.

THE PROPHYLACTIC USE OF A MOLYBDENUM-IRON COMPLEX* IN PREGNANT PATIENTS

WILLIAM J. DIECKMANN, S.B., M.D., H. D. PRIDDLE, M.D., J. A. KING, M.D.,
AND J. B. FORMAN, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology of the University of Chicago, and
The Chicago Lying-in Hospital)*

THE anemia of pregnancy with a relative (hemodilution) or absolute decrease in the hemoglobin concentration has not been cured by the administration of the usual iron salts. Although several observers have stated that most of the patients with anemia in pregnancy will respond if given adequate amounts of iron, Talso and Dieckmann did not find a significant increase in the hemoglobin concentration of patients so treated. Dieckmann and Priddle, in a recent report, stated that 4.6 per cent of our pregnant patients were anemic according to our standards of pregnancy, but if the standards for nonpregnant patients were used, then 39 per cent were anemic. These latter authors reported rapid and significant increases in the hemoglobin concentration of anemic pregnant patients who were given adequate amounts of a molybdenum-iron complex. Neary, in a previous paper, reported no failures in pregnant patients who were given this special iron salt. Chesley and Annito, in a well-controlled study, also found significant increases in hemoglobin concentration of pregnant patients who were given adequate amounts of this special iron salt.

Our practice is to obtain a hematocrit determination each trimester of pregnancy, at term, and again at six weeks post partum. These periodic determinations have added considerably to our clinic costs. We decided to give a prophylactic dose of three tablets of the molybdenum-iron complex, which is half of the therapeutic dose, to a group of patients beginning about the middle of pregnancy and continuing to term. The patients were taken at random without knowledge of their blood picture, and an effort was made to take an equal number of patients, one for treatment and one for control, each approximately at the same period of gestation. Hematocrit and hemoglobin determinations were made on these patients at approximately two-month intervals, at term, and at six weeks and six months post partum. There were 101 patients in each group, but all were not included in the study because some were anemic, left the clinic, were not cooperative, or the data were insufficient. Sixty-seven patients comprised the final treated group and fifty-six the control. Our data are given in Fig. 1. The number of determinations for each group at the various periods designated was a minimum of thirteen and a maximum of fifty-six. Too few patients returned for the six months' examination. These patients were all from our branch clinic in the Stock Yards neighborhood which was selected because they have the lowest income and, as a result, might be expected to have less adequate diets and therefore to be more likely to have anemia of pregnancy. To our surprise we found that the hemoglobin and hematocrit determinations

*The molybdenum-iron complex (Mol-Iron) was supplied by the White Laboratories, Inc., Newark, N. J.

were higher than in patients with greater incomes in the main hospital clinic. The mean hemoglobin concentration at term in the treated group was 13.1 grams per cent with the values ranging from 11.1 to 15.2 grams per cent. In the control group the mean was 12.2 grams per cent with a range from 10.3 to 14.9 grams per cent. Thirty-nine per cent of the control and 15 per cent of the treated group had a hemoglobin concentration less than 12 grams per cent. Six weeks after delivery the means were almost the same although the treated group was slightly higher than the control. The mean hemoglobin concentration for both groups at term was higher than either the Dieckmann-Priddle (treated, 11.8; control, 10.7) or the Talso-Dieckmann (treated, 10.9; control, 9.7 grams per cent) groups. Means for the hematocrit for treated and control group were 39.5 (range 34 to 45) and 38.1 (range 34 to 45) volumes per cent, respectively. The difference is probably due to the fact that, in the latter two groups, all the patients were anemic during pregnancy.

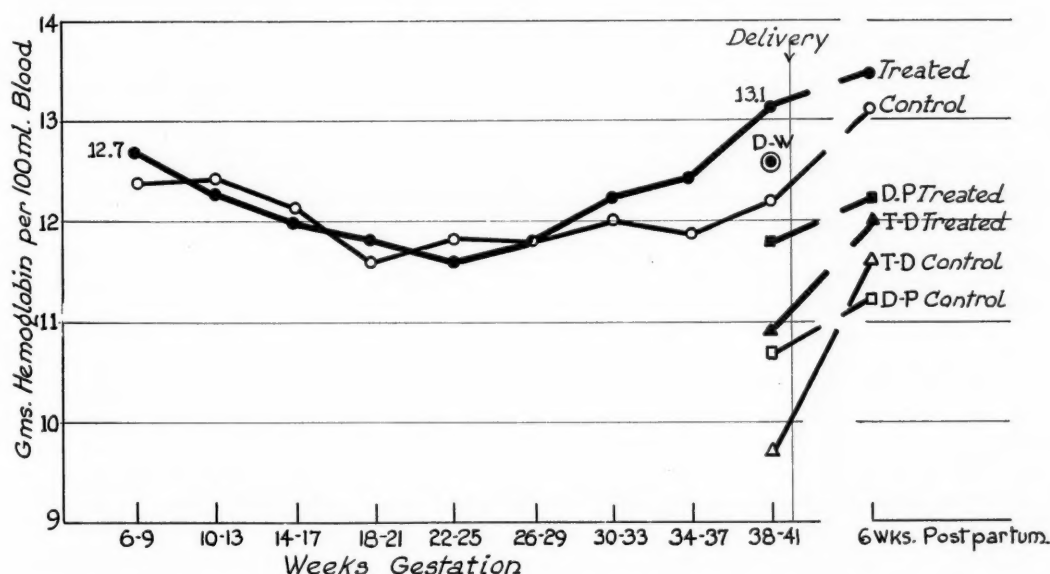


Fig. 1.—Means at 38 to 41 weeks' gestation were all obtained before or early in labor. D-P, Dieckmann-Priddle means; T-D, Talso-Dieckmann means; D-W, Dieckmann-Wegner mean.

We have now started in all our clinics the routine administration of three of the molybdenum-iron complex tablets daily for a period of thirty days beginning sometime between the thirty-second and thirty-fifth week of pregnancy in order that the patient will have taken 100 tablets by term. If we can cause a significant increase in the hemoglobin concentration of most of our patients, we will be able to discontinue some of the laborious and expensive blood analysis which we have deemed necessary. We also wish to state that although we have had adequate nutrition instruction in our clinics since 1945, 39 per cent of our pregnant patients are anemic.

Summary

The routine daily administration of one-half of a therapeutic dose of a molybdenum-iron complex for the last three to four months of pregnancy resulted in a much higher hemoglobin concentration at term than in the control patients.

The same treatment, but for only one month late in pregnancy, has been made a routine procedure for all of our pregnant patients.

References

- Chesley, R., and Annito, J.: Bull. Margaret Hague Maternity Hosp. 1: 68, 1948.
Dieckmann, William J., and Wegner, C.: Arch. Int. Med. 53: 71, 188, 1934.
Dieckmann, William J., and Priddle, H. D.: AM. J. OBST. & GYNEC. 57: 541, 1949.
Neary, E.: Am. J. M. Sc. 212: 76, 1946.
Talso, P., and Dieckmann, William J.: AM. J. OBST. & GYNEC. 55: 518, 1948.

Hoff, Franz: Asphyxia of the Newborn, Wien. klin. Wchnschr. 61: 149, 1949.

Intrapartum and neonatal deaths (2.6 to 5.4 per cent of births) are predominantly due to asphyxia, which may begin at any time during the second stage of labor. Improper obstetric management, including failure to interfere on indication, may lead to profound asphyxial damage and fetal death.

Prolonged and excessive intrauterine pressures during labor can cause brain hemorrhages from pressure alone, with neonatal asphyxia due to respiratory-center damage. Second, during contractions placental blood is forced into the fetus, and there is increased resistance to cord flow toward the placenta. Within limits the fetal heart can overcome this resistance, but slowing of the fetal heart, which appears in 5 per cent of cases, is objective proof that some difficulty is present. Placental circulation and gas interchange are reduced at this time. When contractions are overlong and frequent fetal anoxia may develop, with a secondary weakening of the fetal myocardium and greater susceptibility to brain hemorrhage. Brain damage irritates the vagus nerve, further slowing the heart. Manometric recordings from the severed cord of a first twin show pressure waves rising to 50 mm. Hg, which are magnified by the increased intrauterine pressure following an oxytocic. Fetal blood pressure must reach 75 to 100 mm. to maintain gas interchange. Severe frequent contractions of the late second stage may produce intrauterine pressures of 100 to 150 mm.; hence mild birth anoxia is a common event.

A sudden drop in intrauterine and intraplacental pressure may lead to pooling of fetal blood within the placenta. This may occur when the uterus is relaxed by anesthesia, when the baby is delivered by traction (forceps, or especially breech deliveries) thus creating a partial intrauterine vacuum, and when there is partial cord compression which collapses the thin-walled cord veins and thus further produces fetal anemia. The baby may bleed to death into his own placenta, with birth asphyxia due to anemic anoxia.

Other sources of fetal anoxia are maternal conditions leading to poor uterine blood supply (tetanic uterine contractions, cardiac decompensation, acidosis, pneumonia, toxemia), impaired cord circulation (ablatio placentae, cord knots, cord prolapse), fetal abnormalities (heart anomalies, diaphragmatic hernia, and aspiration of various fluids).

The author recommends prompt delivery at signs of fetal distress, the routine use of an intravenous oxytocic as delivery is begun, and careful aspiration and oxygen administration to the newborn.

IRVING L. FRANK.

DIRECT CONTACT VAGINAL CYTOLOGY SMEAR TECHNIQUE

MORTIMER N. HYAMS, M.D., F.A.C.S., ROBERT G. HYAMS, M.D., AND
EMANUEL E. WAINESS, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University Bellevue Medical Center, University Hospital)

IT IS less than a decade since Papanicolaou introduced the practical use of the vaginal smear as another important diagnostic procedure in the armamentarium of the gynecologist. Today, the histopathological examination of cellular exudate and uterovaginal exfoliation is an established specialty. The cytologist is able to follow accurately the various cyclic changes associated with normal and abnormal ovarian function and often to verify the presence of malignant neoplasms or to discover those previously unsuspected.

Although generally accepted, vaginal smear diagnosis is not yet universally used for two reasons: first, an insufficient number of trained cytologists, and, second, the frequent inadequacy of the smears obtained. We believe that as the importance of this procedure becomes better established, the number of men trained in interpretation of the smears will also increase. The purpose of this paper is to rectify the second obstacle, i.e., to obviate the inadequate smear.

Two methods of obtaining the vaginal detritus and exfoliation for the slide are used:

A. The pipette method wherein vaginal secretions are aspirated and then transferred to a slide for examination.

B. The spatula method wherein surface cells are scraped from areas of suspected or potential malignancy, especially the cervix, for transfer to slides.

The second method or "surface biopsy" technique has been employed by us when the paucity of vaginal exudate made aspiration unfeasible, or when we desired a specimen from a localized lesion. Even then, it was our feeling that we were testing a specific area or lesion rather than obtaining a cross-section of uterovaginal exfoliation. The first method is adequate in the presence of profuse secretion, but in those cases with scanty or even normal secretion, the most energetic aspiration is frequently disappointing and the resultant smear scanty and quick drying, which is embarrassing to the gynecologist and presents a problem for the cytologist.

It is because of this that we have devised an instrument and perfected a technique to be referred to as the "direct contact smear technique." The instrument consists of a slender metal base or holder, A, into which slips any standard-sized glass slide. There is a slender metal cover, B, which, fitting in a groove over the slide, effectively covers the slide when in position No. 1 and exposes the face of the slide when in position No. 2. Except for length, the entire instrument is barely larger in all dimensions than the glass slide itself.

The technique recommended requires no special positioning of the patient, although the lithotomy position is the one most frequently used. With the holder closed, i.e., in position No. 1, covering the enclosed slide, it is gently inserted obliquely into the vaginal orifice. Once past the introitus, the instrument is turned so that the upper surface, i.e., the portion referred to as B, is in contact with the posterior vaginal wall. This is verified by the position of the

"star" on the proximal anterior surface of the holder. With the instrument deep in the vagina the handle, C, is pulled out, causing the instrument to assume position 2. The face of the glass slide is now in direct contact with the posterior wall of the vagina. At this point the patient may be asked to strain, which, with the instrument in position causes the mucosal folds to be pushed in apposition to the slide, or a finger may be inserted in the rectum and with a massaging motion the posterior wall of the vagina pressed against the face of the glass slide. The handle, C, is then pushed in, returning the instrument to position 1 or closed. The instrument, with the glass slide thus protected, is withdrawn from the vagina. The slide is then extruded from the holder, its under surface clean and dry and its upper surface copiously covered with exudate which is evened and thinned by running the edge of a glass slide over it in the manner employed for making blood smears. The instrument is easily cleaned, sterilized, and is ready for use after a new slide has been inserted.

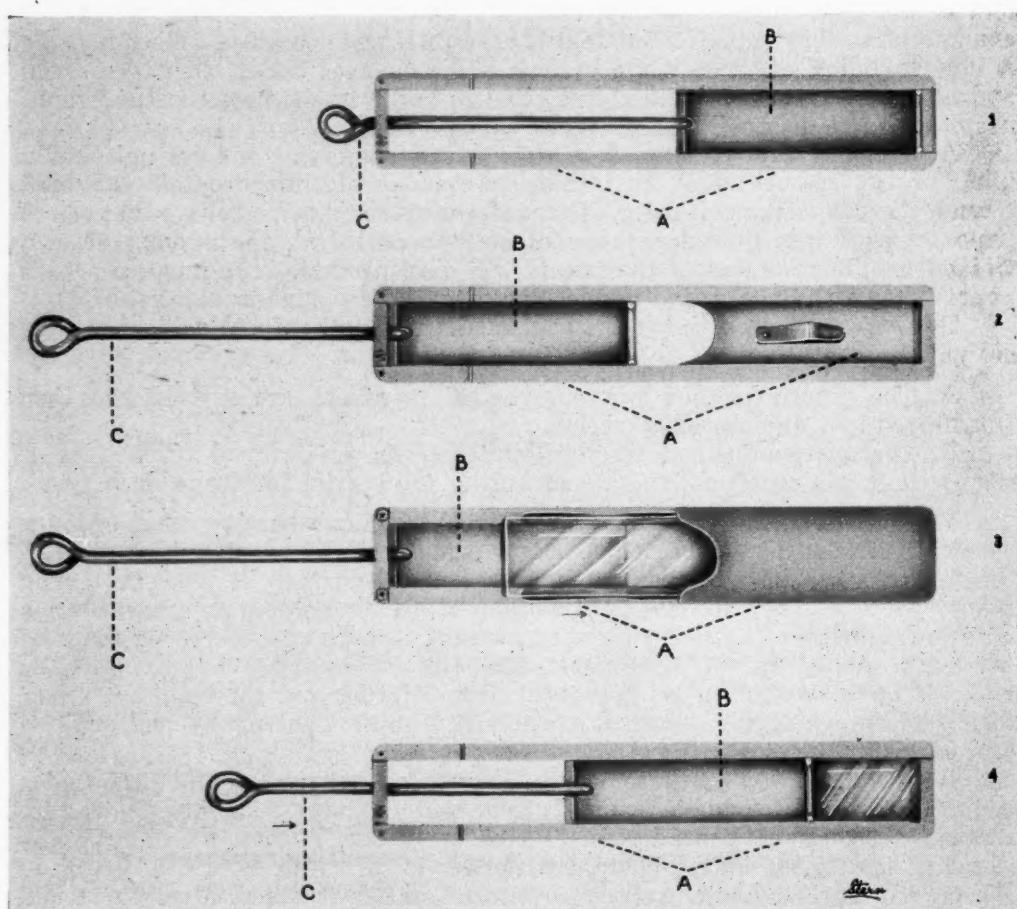


Fig. 1.—1, Instrument closed, showing anterior surface. 2, Instrument open, viewed from anterior surface. 3, Instrument open, viewed from posterior surface, as glass slide is being inserted. 4, Instrument partly open, as seen from the anterior surface, exposing part of the enclosed glass slide.

A, Holder, with star seen on its proximal anterior surface. B, Sliding cover. C, Handle.

Because of the normally collapsed nature of the vaginal cavity wherein the anterior and posterior walls are usually in apposition, we have felt that exudate found on the surface of the posterior wall will, in the greater number of in-

stances, reflect the cytology of the entire cervical and vaginal desquamation. We have, however, obtained smears from the anterior wall by merely reversing the position of the instrument, having the exposed slide face up and having the patient "bear down" with or without suprapubic pressure.



Fig. 2.—Cross section of pelvis, showing the instrument open in the vagina, finger in rectum, bringing the posterior vaginal wall in contact with the slide.

The advantages of this "direct contact smear technique" are, we believe, quite obvious. A generously covered slide is obtained without trauma. The instrument, by virtue of its very small dimensions and rounded edges is easily slipped into the vagina and the smear obtained unadulterated by the mixture of lubricant, etc., that may be attendant upon the insertion of specula. Finally, the sampling of cellular exfoliation reflects the general uterovaginal status.

In summary, an instrument and technique have been introduced for the purpose of obtaining adequate vaginal smears with a maximum of facility.

The instrument is made by: Mooradian High Frequency Laboratories, 137 Park Place, Bogota, New Jersey.

78 EAST 79 STREET

AN ABNORMAL EARLY HUMAN OVUM

WILLIAM E. STUDDIFORD, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, New York University College of Medicine and the Obstetrical and Gynecological Service of the Third [New York University] Surgical Division, Bellevue Hospital)

DURING the past five years a number of observations have been made which have clearly defined a stage of human embryology of which little had been previously known. This advance in knowledge has been largely made by John Rock, a clinician collaborating with Arthur Hertig, a pathologist, and with C. H. Heuser, an embryologist.^{1, 2, 3, 4, 5} By a careful and meticulous examination of human uteri removed at a time when an early pregnancy might be present, twenty-six young embryos have been assembled within a relatively short time. These specimens, with the addition of a few human eggs fertilized in vitro, have enabled these investigators to give an accurate account of the development of the human ovum in the first fourteen days of its existence with the exception of a brief period between the third and the seventh day of embryonic life. No doubt the continued efforts of these collaborators will soon fill in this gap. Several variations have been discovered between the processes of early pregnancy in human beings and those occurring in the rhesus monkey and in the lower animals on whom we were formerly dependent for our knowledge of early embryology. The additional discovery that twelve of the twenty-six specimens (47 per cent) were abnormal was an unexpected finding in this series. Early abortion was about to take place in some of these and could be expected eventually in all. Three of these were discovered prior to nidation. Two of the implanted specimens consisted only of trophoblast. Four have normal embryonic discs but defective accessory structures. One has an adequate chorion but a defective embryo and in two both the embryo and the trophoblast are abnormal.

The specimen which is to be presented belongs to the last division of the latter group. The following is a brief account of the circumstances under which it was discovered.

Mrs. E. P., aged 35 years, married, para ii, gravida ii, was admitted to the Gynecological Service at Bellevue Hospital on Jan. 26, 1948. Her menses had been regular, every thirty days, lasting eight days. The last normal menstruation had occurred about Jan. 1, 1949. Her chief complaint was pain in the lower abdomen and back for some months. A firm, nodular uterus about the size of a twelve weeks' gestation was found on bimanual examination. On February 3, a total hysterectomy was performed for multiple fibroids, approximately four days after her expected menses failed to appear. At the time of operation a large corpus luteum was noted in the right ovary. The fibroid uterus was opened by a midline incision of the anterior wall revealing an endometrial lining almost 1 cm. thick. To one side of the upper part of the incision, and narrowly missed by it, was a small purplish vesicle about 4 mm. in diameter with a shiny surface attached to the surface of the endometrium by a short, thick pedicle (Figs. 1, 2 and 3). On the basis of the patient's history the ovum was thought to be about 17 days of age. Because of the character of its implantation it was suspected of being defective. The vesicle with its surrounding endometrium was excised and sent to Dr. Chester H. Heuser of the Carnegie Institution of Washington.

Microscopic examination of the endometrium showed an advanced progestational change approaching that of true decidua. There was no evidence of any degeneration, necrosis, or deficient vascularization. Dr. Heuser supplied the microscopic details of the ovum. It was about the size one would expect for its age. Its implantation must have been very shallow since instead of lying completely within the mucous membrane as it



Fig. 1.—Excised area of endometrium and myometrium showing lateral view ovum attached by pedicle ($\times 3$).

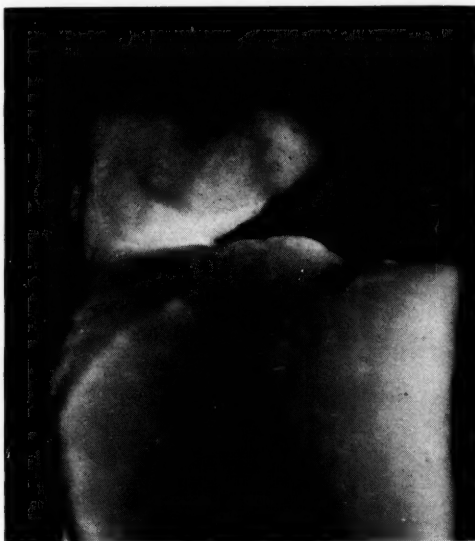


Fig. 2.—Inferior aspect of ovum ($\times 12$).



Fig. 3.—Superior aspect of ovum ($\times 12$).



Fig. 4.—Low power of ovum showing the underlying progestational endometrium.

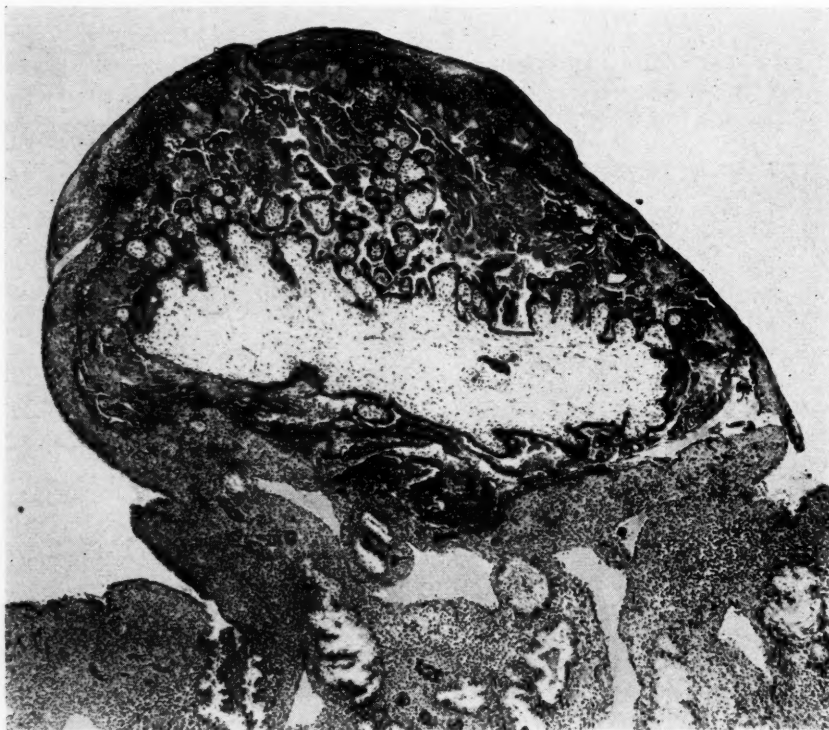


Fig. 5.—High power of ovum showing (a) deficient trophoblast at embryonic pole and active trophoblast at the opposite pole; (b) stunted embryonic disc with early amnion present only in few sections.

should, it had projected its thin covering of decidua outward into the cavity of the uterus (Fig. 4). The trophoblast was scanty and underdeveloped at the deepest or embryonic pole of the ovum; it was abundant with many early villi over the outer or superficial pole. The embryonic disc, embedded in a mass of mesoderm, was much smaller than it should have been, appearing in only a few sections. Its ventral aspect was directed upwards. The anlage of the amnion was present (Fig. 5).

In theory one may trace the possible train of events leading to this abnormality. The trophoblast at the embryonic pole appeared to have been defective, leading to a very shallow nidation. The adequate trophoblast at the opposite pole was being rendered less and less effective in carrying nutrition to the embryo, because the growth and expansion of the ovum was removing this pole further and further from the maternal blood supply. This unusual arrangement of the chorion may well account for the fact that the embryo failed to develop properly. It would seem certain that continued enlargement of the ovum would have led to embryonic death from faulty nutrition and inevitable early abortion.

At the present time there is a great difference of opinion as to whether early abortion occurs as a result of a genetic or an environmental defect. The specimen presented suggests that the former cause is the more likely in this specific instance.

References

1. Rock, John, and Menkin, M. F.: *Science* 100: 105, 1944.
2. Hertig, A. T., and Rock, John: *Anat. Rec.* 94: 25, 1946.
3. Heuser, C. H., Rock, John, and Hertig, A. T.: *Contrib. Embryol.* (Nos. 198-206) 31: 85-100, 1945.
4. Rock, John, and Hertig, A. T.: *AM. J. OBST. & GYNEC.* 47: 343, 1944.
5. Rock, John, and Hertig, A. T.: *AM. J. OBST. & GYNEC.* 55: 6, 1948.

Bickers, William: Stilbestrol in Endometriosis, South. M. J. 42: 229, 1949.

The treatment is reported of 19 cases of extensive pelvic endometriosis with stilbestrol, given in doses of 5 mg. daily from the fifth to the twenty-fifth day of the cycle. In the 19 cases reported, this treatment was given for three consecutive months. Another group of 13 patients is now under treatment on the same plan, which is to be continued for six months. In four of the 19 cases, there were vaginal implants in the posterior fornix, which could be seen through the speculum. In all these cases these purple nodules disappeared under stilbestrol therapy; in one case there has been no recurrence after six months; in one there was a recurrence at four months; the other two patients have not been followed up. In 6 cases, pelvic surgery was done with removal of chocolate cysts or some implants; following surgery the stilbestrol treatment resulted in complete relief of symptoms; all the patients in this group have been followed up, and in six months symptoms recurred in only one case. In 9 cases, the diagnosis of endometriosis was made on the basis of clinical findings without surgery or biopsy. All pelvic pain and other symptoms were relieved during the three months' treatment with stilbestrol; and there has been no recurrence of symptoms in the follow-up period of two to six months. If good results are obtained with a three months' course of stilbestrol treatment of endometriosis, it may be necessary to repeat treatment once or twice a year.

HARVEY B. MATTHEWS

AN IMPROVED TREATMENT FOR TRICHOMONAS VAGINALIS VAGINITIS

JOHN F. FIORINO, M.D., EVERETT, WASH., LOUIS ARRIGONI, PH.D., SEATTLE,
WASH., AND G. A. TOZER, F.A.C.A., EVERETT, WASH.

THE treatment of *Trichomonas vaginalis* vaginitis is a highly controversial problem and the methods of treatment advocated are almost as varied and numerous as the number of gynecologists treating the condition. The various therapeutic agents commonly in use include purported trichomonacidal and trichomonadostatic drugs, douches, dyes, suppositories, tampons, jellies, etc. However, in spite of and because of such a multiplicity of treatments and in view of the abnormally high percentage of recurrences it must be concluded that adequate therapy has not yet been attained.

The treatment proposed herewith was formulated as the result of an extensive series of tests on the vaginal secretions of both infected and uninfected women. This investigation definitely established that the pH of the normal vaginal secretions is 4.0 to 4.5, that lactobacilli are present, and that the nature of the discharge is muco-epithelial. Contrary to this, the pH of the secretions of the parasitized vagina is above 5.0, usually in the range of 5.5 to 6.5, lactobacilli are absent but various other abnormal flora are present along with considerable numbers of leucocytes.

The significant fact derived from these studies was that apparently the trichomonad does not thrive in the pH range of the normal vaginal secretions, and consequently pH change may occur before infection can become established. The rationale of the treatment that is being advocated by the authors is based on the re-establishment and *maintenance* of a normal pH of the vagina, since that is incompatible with survival of the trichomonads and the abnormal flora associated with them, and is desirable for the growth and reproduction of the lactobacilli which help to produce the normal reaction of the vaginal secretions.

The change in reaction of the vaginal fluids was achieved by the use of an acid douche, which decreased the pH to within the normal range, and was then followed by a strongly buffered tablet insert which served to maintain this pH over a long period of time. The pH of the parasitized vagina prior to and during the course of the treatment was accurately determined by means of a Beckman pH meter with a specially devised glass electrode which was inserted deeply into the vagina while the calomel electrode was placed near the urethral orifice, taking care that sufficient fluid was present to constitute a suitable bridge.

The acid douche which has proved highly satisfactory has the following composition:

Glycerin	4 oz.
Lactic acid	½ oz.
Phosphoric acid	½ oz.
Solution phenylmercuric nitrate 1:1000 q.s.	1 pt.

One tablespoonful of this solution added to one quart of warm water was used as a douche morning and evening. The pH of this solution is 3.6.

The purpose of this douche is trifold. It serves to cleanse the vagina of the variegated microbial population that it harbors in trichomoniasis; it serves to a limited extent as a trichomonacide and finally the lactic and phosphoric acids function in the restoration of the normal pH of the vagina. The phosphoric acid is an improvement over the more commonly used acetic (vinegar), citric, and other acids because it is a strong acid and as such resists an immediate large reduction in hydrogen-ion concentration when subjected to partial neutralization.

The acid douche was followed by the use of the previously mentioned buffered acid inserts which are made from the following formula:

Potassium phosphate monobasic	200.00 c.c.
Phosphoric acid 85%	15.00 c.c. or q.s. to pH 3.6
Carbamide hydrochloride	0.04 c.c.
Beta lactose	200.00 c.c.

Compressed tablets weighing 2.75 Gm. of pH 3.6 when dissolved in one quart of water are made from this mixture. The patients were instructed to insert one tablet deeply into the vagina every six hours and to use two at night, thus insuring a constant and prolonged effect.

In this instance the buffering agents used are phosphoric acid, the same buffer acid as employed in the acid douche, and monobasic potassium phosphate, both strong buffers which stubbornly resist an increase in pH due to the formation or addition of alkaline compounds.

In addition to possessing high buffer capacity these inserts also have adequate trichomonacidal power, are nontoxic, highly hygroscopic, and exhibit marked tissue penetrability due to the incorporation of a wetting agent which reduces the surface tension of the vaginal fluids.

The net therapeutic effect of these inserts then is to maintain the pH of the vagina restored to the normal level by the acid douche, to dry the vagina, to promote penetration of the vaginal folds and to exert a trichomonacidal effect. All of these factors synergize the destruction of the trichomonads and bring about a regeneration of the natural vaginal flora which helps to maintain it in its normal healthy condition.

Therapeutic Effectiveness

This treatment has now been used on three hundred cases of *Trichomonas vaginalis* vaginitis with excellent results.

In this series of patients the vaginal reaction prior to medication had a pH range of 5.2 to 6.6 with the average about 6.0. Subsequent to the institution of treatment the pH in most instances dropped to about 4.2 in less than one week. In addition to the restoration of the normal acidity, trichomonads disappeared, only scattered leucocytes and abnormal bacteria were found, whereas the lactobacilli and epithelial cells reappeared in the vaginal secretions. The purulent discharge, inflammation, and pruritus disappeared concomitantly with the re-establishment of the normal vaginal conditions.

It was found that in most cases a complete cure could be effected in about seven days. However, a sufficient number of patients still showed the presence of trichomonads at the end of one week to make it advisable in all cases to carry on treatment for two weeks, at the end of which time the complete absence of trichomonads was exhibited in all instances and the pH of the vagina was in the normal range of 4.2 to 4.5.

The number of recurrences to date has been insignificant, something less than 4 per cent, all of which were easily cured by the reinstatement of therapy for a short period of time.

Of the 300 cases treated with this method, the following results have been obtained:

Complete cures without recurrence	268
Cures after recurrence	11
Results unknown	21

Summary

1. Three hundred cases of *Trichomonas vaginalis* vaginitis have been subjected to a new form of therapy involving the use of buffer acid douche to lower the pH to the normal range followed by an insert composed of acid buffer salts and a wetting agent which maintains the normal vaginal acidity.

2. This treatment results in the rapid and efficient cure of trichomoniasis with practically no recurrence.

3. Of the 279 of the original 300 patients who returned for re-examination, 268 were cured without recurrence and the remaining eleven were cured after an additional period of treatment following recurrence.

Conclusions

Since it has been shown that *Trichomonas vaginalis* will not thrive in the normal vaginal pH (4.0 to 4.5) and in the presence of lactobacilli, it follows that elimination of the parasites and cure of the trichomoniasis can be effected by restoring these conditions in the vagina. This can best be achieved by the selection of the proper combination of acid douches and buffers supplemented by a suitable wetting agent, to increase the penetrability of the medicaments into the tissue folds.

The therapy advocated by the authors embodies these principles as evidenced by the fact that following its use as indicated, the trichomonads disappear, the vaginal reaction returns to the normal pH 4.2 to 4.5, and the normal flora reappears.

The results described in this preliminary report of 300 cases are extremely encouraging although additional work will be necessary to establish the absolute validity of this treatment.

AN ANESTHETIC TECHNIQUE FOR CULDOSCPIC EXAMINATION

Preliminary Report

ALBERT DECKER, M.D., WAYNE DECKER, M.D., AND JACK MILOWSKY, M.D.,
NEW YORK, N. Y.

(From the Departments of Gynecology and Anesthesiology, Knickerbocker Hospital)

THE value of culdoscopy has been demonstrated.¹⁻⁵ At the Knickerbocker Hospital this procedure is frequently utilized to aid in the differential diagnosis of pelvic diseases. It has been useful in the diagnosis of pelvic tumors, inflammatory lesions, ectopic pregnancies, endometriosis, and in infertility studies. Details of culdoscopic examination have been described elsewhere.^{1, 2, 3, 5} Briefly, the procedure is as follows:

The patient assumes the knee-chest position and is supported by upright leg holders and shoulder braces. Vulva and vagina are cleansed. The cervix is grasped with a vulsellum. The site of the puncture in the vaginal vault is infiltrated with 3 to 4 c.c. of 2 per cent procaine and the puncture is made with the trocar and cannula. After the trocar is removed, the culdoscope is inserted and the pelvic organs are visualized. Suprapubic pressure, traction, and manipulation of the cervix facilitate complete visualization.

Certain considerations have become apparent in the examination of more than four hundred women since the beginning of the utilization of culdoscopy at this hospital. While the examination may be accomplished at times with little or no local anesthesia, some patients complain of discomfort associated with the examination. It is this problem we wish to consider.

In an attempt to evaluate the complaint of pain, certain facts become obvious. The patients with acute peritoneal irritation object to the slightest manipulation of pelvic organs. Women with ruptured tubal pregnancies will seldom tolerate bimanual pelvic examination. Varying degrees of discomfort to the examination have been noted in women with chronic pelvic infection. In the culdoscopic examination of apprehensive, hypersensitive, and emotionally unstable individuals, discomfort may be a prominent feature.

Local infiltration of the vaginal mucous membrane gives inadequate pain relief in many of the above patients. Thus, more complete and accurate diagnosis is facilitated and enhanced in some individuals by the utilization of a satisfactory anesthetic technique. Several considerations must be satisfied. Culdoscopic examination is of short duration and may be done on ambulatory patients. The procedure necessitates the presence of voluntary muscle action of the patient in assuming and maintaining the knee-chest position. Obtundation of consciousness requires careful and vigilant maintenance of a patent airway. Adequate ventilation in an unconscious patient in the knee-chest position is generally unsatisfactory and difficult unless an endotracheal airway is estab-

lished. Techniques are feasible employing subarachnoid injections with hypobaric and hyperbaric agents. Fixation of agents at the desired level and maintenance of circulation must be controlled carefully. Epidural injections have been utilized in some cases. Common and frequent anomalies of the sacrum may preclude routine usage of this method of analgesia. In addition, considerable skill and care must be exercised.

At Knickerbocker Hospital, patients who require anesthesia for culdoscopic examination are given subarachnoid injection of small amounts of dilute procaine solution. An attempt is made to secure sensory rather than motor anesthesia (Sarnoff, Arrowood, and Chapman⁶). The patients are positioned to obtain a saddle type of anesthesia (Adriani⁷).

Twenty-five to 50 mg. of 2.5 per cent procaine solution are injected at a uniform rate (1 c.c. in five seconds) into the subarachnoid space in the interspace between the fourth and fifth lumbar vertebrae, while the patient maintains the sitting position. A 20 gauge needle is employed. The patient remains in the sitting position for five minutes. Following this period, the patient may voluntarily assume the knee-chest position and examination may proceed. Contraindications to the technique are the same as those which are listed for spinal anesthesia.

Twenty-five patients requiring culdoscopic examination or minor operative procedures involving the perineum were anesthetized by this technique. The results were as shown in Table I.

TABLE I

	AGE	DOSE	PRE-MEDICATION	DURATION OF ANESTHESIA	RESULT	PROCEDURE
1.	19	40 mg.	No	25 minutes	Good	Culdoscopy
2.	22	30 mg.	No	25 minutes	Good	Culdoscopy
3.	43	25 mg.	Yes	30 minutes	Excellent	Culdoscopy
4.	34	25 mg.	Yes	25 minutes	Good	Culdoscopy
5.	30	25 mg.	Yes	25 minutes	Excellent	Culdoscopy
6.	28	25 mg.	No	20 minutes	Excellent	Dilatation and curettage
7.	46	25 mg.	Yes	20 minutes	Good	Culdoscopy
8.	25	25 mg.	Yes	30 minutes	Excellent	Culdoscopy
9.	30	30 mg.	No	25 minutes	Good	Culdoscopy
10.	48	30 mg.	Yes	25 minutes	Excellent	Culdoscopy
11.	33	25 mg.	Yes	30 minutes	Excellent	Culdoscopy
12.	30	30 mg.	Yes	25 minutes	Excellent	Culdoscopy
13.	39	25 mg.	No	30 minutes	Good	Culdoscopy
14.	24	30 mg.	Yes	15 minutes	Fair*	Culdoscopy
15.	32	25 mg.	Yes	25 minutes	Excellent	Culdoscopy
16.	26	30 mg.	Yes	30 minutes	Fair†	Culdoscopy
17.	21	30 mg.	Yes	35 minutes	Excellent	Culdoscopy
18.	28	25 mg.	Yes	20 minutes	Good	Culdoscopy
19.	25	30 mg.	Yes	30 minutes	Excellent	Hemorrhoidectomy
20.	36	30 mg.	Yes	25 minutes	Excellent	Cautery of cervix
21.	20	25 mg.	Yes	20 minutes	Excellent	Posterior colpotomy
22.	37	30 mg.	No	20 minutes	Excellent	Culdoscopy
23.	50	25 mg.	Yes	20 minutes	Good	Dilatation and curettage
24.	30	25 mg.	Yes	30 minutes	Good‡	Culdoscopy
25.	39	50 mg.	No	25 minutes	Fair	Culdoscopy

*Anesthesia at level of D-12.

†Four minims Neo-Syneprine, intramuscularly, for fall in blood pressure.

‡Headache for two days postoperatively.

Discussion

Initial manipulation, cul-de-sac puncture, and insertion of the culdoscope were completed without discomfort in all of the patients in this series. In ten patients, discomfort was experienced after the examination had been in progress for twenty to twenty-five minutes. The pain, which was vague in character and location, was generally referred to the epigastrium or right or left upper quadrants. Frequently, the examinations were prolonged in order to obtain photographs of the existent pathology.

A "saddle" type of anesthesia was obtained in twenty-four patients. In one patient, the level of anesthesia was found to be at D-12. At no time was paralysis of the lower extremities noted. A vasopressor was used in one instance when the systolic blood pressure fell from 100 to 70. A prompt response was obtained with 4 minims of Neo-Syneprine intramuscularly. The procedures lasted from twenty to forty-five minutes. In four patients requiring operative procedures of the perineum, satisfactory analgesia was noted.

One postoperative complication was reported. Severe headache lasting for two days was found in a patient who was culdoscoped to facilitate the diagnosis of an ectopic pregnancy. This patient had a general anesthesia for dilatation and curettage immediately following culdoscopy.

Conclusion

Satisfactory analgesia for culdoscopic examination may be obtained by the injection of small amounts of dilute procaine solution subdurally. Patients with intra-abdominal pathology (inflammatory lesions, tubal pregnancy, etc.) may experience discomfort on manipulation of the culdoscope if the procedure is prolonged. This technique and agent are of value in operative procedures of short duration involving the perineum. Sensory anesthesia alone may be obtained.

Summary

The results of the use of dilute solutions of procaine subdurally in twenty-five patients requiring culdoscopy or minor operative procedures around the perineum have been reviewed.

References

1. Decker, A., and Cherry, T. H.: *Am. J. Surg.* **74**: 40, 1944.
2. Decker, A.: *Am. J. Surg.* **83**: 313, 1947.
3. Decker, A.: *Pelvic Culdoscopy*, in Meigs, J. V., and Sturgis, S. H., editors: *Progress in Gynecology*, New York, 1946, Grune & Stratton, Inc., p. 95.
4. Decker, A.: *New York State J. Med.* **46**: 314, 1946.
5. Telinde, R. W., and Rutledge, F.: *AM. J. OBST. & GYNEC.* **55**: 102, 1948.
6. Sarnoff, Stanley, Arrowood, Julia G., and Chapman, William P.: *Surg., Gynec. & Obst.* **86**: 571, 1948.
7. Parmley, R. T., and Adriani, John: *AM. J. OBST. & GYNEC.* **52**: 636, 1946.

THE USE OF NIDOXITAL IN EMESIS GRAVIDARUM

FRANK R. HURLBUTT, M.D., GREENWICH, CONN.

(From the Greenwich Hospital)

PERHAPS the most frequent, although generally not serious, complication of pregnancy is emesis gravidarum. The actual etiology of this difficulty has been frequently hypothesized but remains unproved. Schoeneck¹ postulates a direct relationship between endocrine activity and hyperemesis, and has reported a higher concentration of gonadotropic hormones demonstrable in the urine of pregnant women having hyperemesis than in normal pregnant women. Many hold to the belief that emesis gravidarum is principally neurogenic in origin; or at least that there is a dividing line between those cases which are neurogenic, and those of more serious nature which seem to stem essentially from a true toxicity. However, regardless of etiology, a patient with emesis gravidarum may be expected to have, in either a mild or severe form, depending on the severity of symptoms, dehydration and some degree of avitaminosis, and must be treated with these facts in mind.

General suggestive therapy is many times effective, and this would seem to bear out the neurogenic theory; but it is interesting that at no point has there been developed a 100 per cent effective regime based entirely on suggestive therapy methods. Bertling² reports 1,008 cases in patients who were interviewed, and found that approximately 700 had parallel symptoms between nausea and vomiting and dysmenorrhea which could very well be psychogenic since there is no obvious common anatomic or physiologic relationship known.

Titus³ believes that "nausea and vomiting of pregnancy is largely unnecessary," and "it can usually be prevented or quickly checked in its early stages by appropriate measures."

"Appropriate measures" may extend from therapy carried out on a purely psychogenic basis to that consisting of high dosages of drugs which have proved efficacious in the treatment of emesis gravidarum. On the theory that nausea in pregnancy is the result of a high concentration of chorionic gonadotropin in the serum, Eller and Randall⁴ felt that increased elimination of this substance by forced hydration should lower the concentration below a theoretical "nausea threshold." The authors believed the reduction in concentration of chorionic gonadotropin by diuresis explained the effectiveness of the forced hydration treatment.

The importance of hydration and dehydration as vital factors in vomiting of pregnancy is well established. Emesis, naturally, involves loss of body fluid to a greater or lesser degree, depending on its severity. When emesis is marked,

dehydration follows, and the latter produces a state of acidosis, which in turn encourages more vomiting. To alleviate emesis, this cycle must be broken, and this is usually accomplished intravenously when fluids cannot be tolerated by the patient orally.

Fully realizing the many facets to this problem, a comparatively new drug, Nidoxital, was used in a series of eighty cases of emesis gravidarum, varying from mild to moderately severe. In a previous series of one hundred cases (not reported) followed by the author at the Methodist Hospital, Brooklyn, N. Y., pyridoxine hydrochloride was given orally, 25 mg. three times a day, and found to be totally effective in 70 per cent of the cases, partially effective in 15 per cent, and ineffective in 15 per cent. Pyridoxine hydrochloride alone has been widely used both orally and parenterally in nausea and vomiting of pregnancy, with varied success.

Of the eighty cases where Nidoxital was used, one patient got no relief because she "couldn't swallow pills"; one patient obtained relief of vomiting but maintained her nausea; and one patient received no relief following the usual advised dosage of one capsule three times a day one-half hour before meals. Seventy-seven patients reported complete remission of symptoms usually within twenty-four to seventy-two hours. No attempt was made to use this drug in cases of marked symptoms only, but each patient was asked if she were experiencing nausea and vomiting at any time. If the answer were in the affirmative, Nidoxital was given routinely.

It is well known that several important and dramatic changes occur in the physiology and pathology of the body outside of the actual genital tract during pregnancy. This is true especially in organs concerned with metabolism. Nidoxital contains elements which tend partially to counteract many of these metabolic changes, and, with the ensuing relief of symptoms, the patient subjectively responds well, so that frequently she may throw off her nausea and vomiting. Pyridoxine hydrochloride, the mainstay of most antiemetic preparations given during pregnancy, is present in Nidoxital in the amount of 50 mg. where it is combined with:

(a) Nicotinamide	25 mg.
(b) dl methionine	100 mg.
(c) Benzocaine	100 mg.
(d) Pentobarbital sodium	15 mg.

No untoward side effects were noted from Nidoxital during this series.

Discussion

The problem of emesis gravidarum is discussed from its etiological and therapeutic approaches, with special reference to the use of a comparatively new drug, Nidoxital, in the control of this problem. While excellent success was obtained in the present series, I do not feel that Nidoxital alone is the complete answer to this common condition. Any intelligent regime to control emesis gravidarum must also incorporate adequate suggestive therapy and medical therapy, based on the knowledge that certain deficiencies in metabolism, hydration, and vitamin intake must necessarily occur.

Summary

Nidoxital was used in eighty cases of nausea and vomiting during pregnancy. Seventy-seven out of the eighty patients reported that they received complete remission of symptoms within twenty-four to seventy-two hours. One patient would not take the medication; one patient was relieved of her vomiting but maintained her nausea; and one patient reported no relief.

The drug discussed in the above article was supplied by the Ortho Pharmaceutical Corp., Raritan, N. J. I have been assisted in its application by Dr. Payson B. Ayres and Dr. Anthony Balchunas. I wish to express my appreciation of their respective contributions.

References

1. Schoeneck, F. J.: AM. J. OBST. & GYNEC. 43: 308, 1942.
2. Bertling, M. H.: AM. J. OBST. & GYNEC. 56: 733, 1948.
3. Titus, Paul: The Management of Obstetric Difficulties, ed. 3, St. Louis, 1945, The C. V. Mosby Company, Chap. XIV.
4. Eller, W. C., and Randall, J. H.: AM. J. OBST. & GYNEC. 50: 518, 1945.

Bonney, Victor: Wertheim's Operation in Retrospect, The Lancet, p. 637, 1949.

In this essay Bonney reviews the history of the Wertheim operation for cervical carcinoma, and his own extensive experience in over 500 cases. Analysis of his results, previously published in twelve papers from 1908 to 1941, shows an over-all operability rate of 63 per cent, and in his private patients of over 80 per cent. He considers any reasonable possibility of removal an adequate criterion of operability. A large number of the so-called Stage III cases can be operated on, and he feels that classification of the disease into stages is likely to be misleading in evaluation of results. Results are more significantly expressed in cure rate per 100 unselected cases.

The immediate operative mortality is formidable, falling somewhat with increasing surgical experience: 20 per cent for his first 100 cases, 14 per cent for the next 200, and 11 per cent for the last 200. Further reduction in operative mortality should accompany the use of modern surgical adjunct therapy. Most of the deaths occurred in patients with advanced disease, and hence an improved immediate survival rate did not materially improve the five-year cure rate.

The corrected five- and ten-year cure rates were 43 per cent and 36 per cent. In 40 per cent of the 500 cases the glands were involved, and in this group the rates were 22 per cent and 18 per cent, while in group in which the glands were free of carcinoma the rates were 58 per cent and 49 per cent. Since the longest period of observation between operation and death from recurrence was eight years, a patient who survives ten years may be regarded as 100 per cent cured. These rates have remained uniform throughout Bonney's career, and are substantially the same as those of Wertheim, Berkeley, Shaw and others.

Bonney states that comparison of radiological and surgical statistics is exceedingly difficult since reports are not on similar groups of cases, and are not impartially presented. The only accurate comparison should be between the results of the pure radiologist and those of the surgeon who operates on some of the patients presenting themselves, and irradiates the remainder. In certain cases surgery, and in others radium would give the best chance of cure, but investigatory methods are too coarse for accurate discrimination. Cases refractory to radium, or beyond its scope should be treated by surgery.

IRVING L. FRANK.

DIETHYLSTILBESTROL IN NAUSEA AND VOMITING OF PREGNANCY

A Preliminary Report

M. H. BERTLING, M.D., AND JOHN C. BURWELL, JR., M.D., GREENSBORO, N. C.

(From the St. Leo's and Sternberger Hospitals)

IN 1941 the Smiths,¹ investigating the metabolism of estrogen and progesterone, were of the opinion that estrogens per se were not responsible for the progesterone-stimulating effect of estrogen, but that the estrogen oxidation products were responsible for this stimulation. Their supposition was that this was effected by pituitary stimulation in the nonpregnant, and through the increased utilization of chorionic gonadotropin in the pregnant patient. They further concluded that stilbestrol evokes an increased secretion of progesterone in pregnancy by initiating an increased utilization of chorionic gonadotropin.

We are publishing this preliminary report because we feel that for the first time a therapy is being proffered which treats the syndrome from an etiological standpoint rather than on a psychogenic basis. One of the authors² had an article recently published on the psychic aspect of nausea and vomiting, but before this article appeared in print we were already using diethylstilbestrol in the treatment of nausea and vomiting. Then, O. W. Smith's³ article on the use of stilbestrol in the treatment of threatened abortion, premature delivery, the complications of late pregnancy, etc., appeared and we were sure from her statement of the basis for the use of stilbestrol in therapy that we were on the right track in our use of the drug for nausea and vomiting on the same etiological basis.

Accordingly, beginning on Oct. 23, 1948, stilbestrol therapy was instituted in those prenatal patients in our practice who complained of nausea and/or vomiting of pregnancy. No other supportive measures were employed in order that the drug might stand or fall, as far as possible, on its own merits.

Complaints were unsolicited; but when the patient volunteered the presence of nausea as a factor in discomfort, therapy was instituted. Five milligrams of diethylstilbestrol orally each day were administered without any attempts at psychotherapy or other supportive measures. This dosage is sufficient quite frequently to initiate nausea in the nongravid female.

Thirty-one patients received this medication, eighteen primigravidas and thirteen multigravidas. Treatment was instituted at the time of the first complaint, in this series ranging from the eighth week through the fifteenth week, one-half being started from the ninth through the eleventh weeks of gravidity. Results appeared in the vast majority by the end of the first week of therapy. Twenty-two patients, or 70 per cent, obtained complete relief and were classed as cures. Eight patients, or 26 per cent, showed marked improvement and no longer complained of discomfort. One patient out of the thirty-one failed to show any definite beneficial response.

Summary

Thirty-one cases of nausea and vomiting of pregnancy have been treated solely by the oral administration of diethylstilbestrol.

Complete relief or marked improvement was obtained in thirty cases, or 96 per cent.

Conclusions

From the standpoint of etiology, there is definite logic in the use of diethylstilbestrol in the treatment of nausea and vomiting of pregnancy, since by causing an increase of progesterone secretion, the utilization of chorionic gonadotropin is facilitated.

Clinical application of this theory, even in so small a series, seems to bear out the logic of this therapy.

References

1. Smith, O. W., Smith, G. V., and Schiller, S.: J. Clin. Endocrinol. 1: 461, 1941.
2. Bertling, M. H.: AM. J. OBST. & GYNEC. 56: 733-737, 1948.
3. Smith, O. W.: AM. J. OBST. & GYNEC. 56: 821-834, 1948.

Fana, C.: Hyperprolanism and Decidua Tuberosa Papulosa of the Endometrium, Folia gynaec. 43: 113, 1948.

According to Virchow, the above is the name given to special polypoid excrescences of the decidua vera seen in rare instances of early abortions. The author describes six cases observed in nonpregnant women whose ages ranged from 41 to 47 years and who were operated upon for other gynecological pathology assumed to be the cause of metrorrhagia.

The most salient characteristic of these cases was the multiple lutein and follicular cysts seen in the ovary, probably denoting an abnormal pituitary function. Another feature was the menometrorrhagia occurring premenopausally.

The basic etiology presumably deals with increased secretions of prolone B and subsequent formation of persistent corpora lutea, cystic or otherwise. In these conditions there is also believed to be an original hyperactivity of Prolone A which causes endometrial hyperplasia with cystic changes. In addition, a feature common to the six cases described deals with local factors, such as chronic metritis and submucous myomas, which probably interfere with local shedding of the endometrium during menstruation. That local factors are important in the pathogenesis of decidua tuberosa papulosa is verified by the work of Loeb, who produced similar lesions by inserting horsehair in the uterine cavity of animals treated with progesterone.

Reference is made to the work of Zondek, showing that hypergonadotropinism can occur in premenopausal women to such an extent that a positive Aschheim-Zondek test may be obtained. Reference is also made to the work of Traut and Kuder in regard to irregular endometrial ripening where the pathogenesis deals more with local endometrial dysfunction rather than with total dysfunction due to hormonal imbalance.

The authors conclude that decidua tuberosa papulosa formerly described only in the gravid women may also be found in the nonpregnant state as a result of hyperactivity of the anterior pituitary. The anatomical basis is on the one hand the follicular and lutein cysts of the ovary, and, on the other, the endometrial picture of cystic glandular hyperplasia combined with an abnormal secretory phase of the type seen in the so-called pseudo decidua observed wherever there is a persistent corpus luteum effect.

ANDREW A. MARCHETTI.

THE PERINEAL CUP IN EPISIOTOMY, PERINEAL AND RECTAL SURGERY

RAYMOND S. HOLTZ, M.D., HARTFORD, CONN.

ALTHOUGH the problem of analgesia in childbirth has been solved most satisfactorily, it is a fact beyond question that many obstetrical patients still suffer considerable pain caused by episiotomy. It is also true that insufficient care is given these patients, not because of willful neglect but because of unintentional carelessness.

Many obstetricians do not examine a perineum from the time the patient leaves the delivery table until the time of the postpartum examination at their offices. The writer has long felt that the armamentarium consisting of hot sitz baths, reading-lamp heat, aspirin, codeine, and analgesic ointment could well be supplemented by the use of the perineal cup pictured herein.

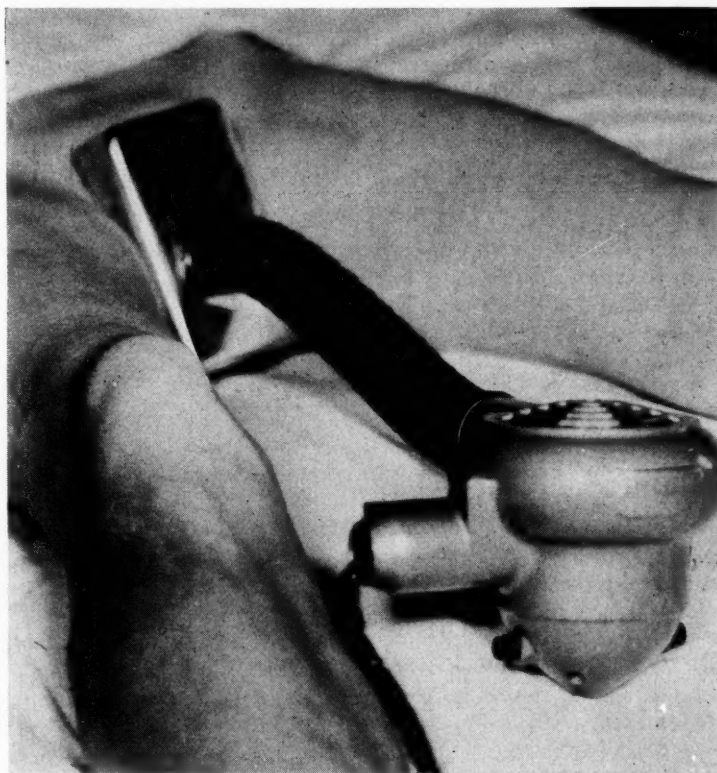


Fig. 1.

It has been found that the maximum amount of benefit is derived from the use of this cup especially when its early use is employed. The circulating air with variable temperature serves not only to allay pain and discomfort but also serves as a drying medium to stimulate more rapid formation of scar tissue in the incision.

The perineal cup finds its place not only in the obstetrical field but in perineal and anal surgery where pain and healing factors are so extremely important. A most desirable feature lies in the fact that the air temperature can be varied to suit the individual desire of the patient, some deriving more benefit from warm air than from cold air and vice versa. Inasmuch as the lochia and heat between the thighs have a tendency to create a wet area around the sutures, the perineal cup by virtue of its drying influence serves to overcome this undesirable condition, and to promote the formation of healthy scar tissue.

In preparing the patient for the perineal cup application the nurse in attendance should carefully wash the vulvoperineal field with green soap solution and dry the area thoroughly with absorbent cotton. The cup should then be applied using both temperatures to begin with, warm at first then followed by cold; the purpose of this is to ascertain from the patient which temperature is most desirable to use. Treatment should be instituted at least twice daily. A fifteen-minute application should be sufficient not only to afford relief to the patient but to stimulate the formation of scar tissue. Following the treatment Surfacaine powder should be applied to the healing area by a powder blower.

In rectal surgery, especially hemorrhoidectomies, the patient occasionally finds more relief in the prone position than in the recumbent position. In the latter use, however, it is often well to employ a roll of gauze placed carefully between the buttocks in order to insure a more direct contact of circulating air with the operative field. In the case of the patient who has undergone rectal surgery, cool air seems to afford more relief than the warm air, whereas in episiotomy and perineal cases the reverse holds true.

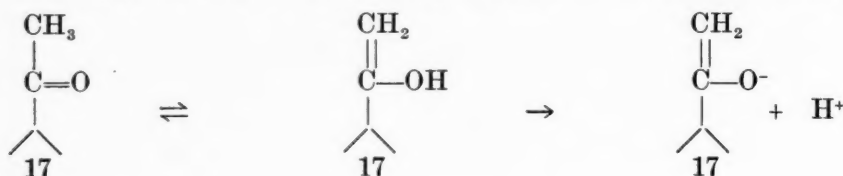
Although application for fifteen-minute periods seems to be adequate in most cases there is no contraindication for more frequent and longer use. The use of the perineal cup for the most part obviates the necessity of placing the patient in the hot bath, which from the practical standpoint would have a tendency to soften or dissolve already formed scar tissue. The analgesic effect of this circulating air also makes the employment of ointments quite unnecessary.

Aside from the stimulation to healing and the analgesic effect to local tissues, the employment of the perineal cup seems to exert a decidedly favorable effect on the patient from a psychological standpoint.

7 WOODLAND STREET

Erratum

In the article, "The Bactericidal Action of Beta Progesterone," by Marie L. Koch, in the January, 1950, issue of the JOURNAL, p. 170, the chemical formula should be as follows:



Department of Reviews and Abstracts

Selected Abstracts

Anesthesia, Analgesia

Brown, J. M., Volpitto, P. P., and Torpin, R.: Intravenous Demerol-Scopolamine Amnesia During Labor, *Anesthesiology* 10: 15, 1949.

A Demerol-scopolamine solution was given during labor to 100 patients, including seven delivered by cesarean section and one delivered by version and extraction, for whom an inhalation anesthetic was subsequently used, the intravenous Demerol-scopolamine serving as premedication. The solution used contained 10 mg. of Demerol hydrochloride and 0.064 mg. (1/1,000 grain) of scopolamine per cubic centimeter; it was freshly prepared for each patient. The initial dose, given at the time of onset of true labor, was 8 to 10 c.c. of this solution for those who had been given no other drugs and 5 to 7 c.c. for those who had previously been given central nervous system depressant drugs. Multiparas usually required only one or two injections, but primiparas often required a third injection. The dosage for the second injection was usually 3 to 5 c.c. and for the third 2 to 4 c.c., with but little difference in the dose employed for those who had and who had not been given depressant drugs previously. A fourth injection was given in six cases and a fifth injection in two cases, all long and difficult labors; the dose for these injections was 1.5 c.c. of the solution.

The intravenous Demerol-scopolamine medication had no effect on the course of the first stage of labor; the second stage was often noted to be unusually rapid; the third stage was not prolonged and there was no excessive bleeding. There were no maternal deaths.

In the 75 cases in which Demerol-scopolamine alone was used, only three infants showed apnea; the incidence of apnea was higher when other depressant drugs had been given. There was only one stillbirth in a case in which labor had lasted forty-eight hours before admission to the hospital and Pitocin had been given. Of the 92 patients delivered without any anesthetic, amnesia was excellent in 53.3 per cent, the patients remembering nothing of the labor; and was good in 32.6 per cent, the patients remembering only isolated instances or persons. The degree of analgesia obtained was less; only two patients (2.2 per cent) showed no evidence of pain, 44.5 per cent showed marked relief from pain, and 33.7 per cent some relief; in most cases the restlessness of the mother was markedly reduced during labor. The primary effect of the intravenous Demerol-scopolamine medication during labor, therefore, was the production of adequate amnesia. HARVEY B. MATTHEWS.

Davis, M. M., and Tupper, W. R. C.: Heroin, Demerol and Hyoscine in Labor, *Canad. M. A. J.* 60: 113, 1949.

Three hundred patients were studied and divided into three groups of 100 each. Group A represented the group in which heroin and hyoscine were used, with the hyoscine repeated as necessary; Group B represented the group using Demerol and hyoscine, with the hyoscine repeated as necessary, and Group C represented the group using Demerol and hyoscine, with the Demerol repeated as necessary. Eighty-one per cent of the patients

receiving heroin and hyoscine with repeated doses of hyoscine were classified as obtaining satisfactory relief (labor a vague memory or a pleasant memory with little or no pain) as compared with 68 per cent for the Demerol-hyoscine with the hyoscine repeated and 69 per cent for the Demerol-hyoscine with the Demerol repeated. With heroin-hyoscine and repeated doses of hyoscine, the authors found ten asphyxiated babies, five of which deaths were undoubtedly due to the medication, and in three the medication probably played a part. All of the cases due to the medication were of the marked type of asphyxia. With Demerol-hyoscine and repeated Demerol, the rate was somewhat higher (twelve babies). The rate was the lowest with the Demerol-hyoscine and repeated hyoscine. The greatest amount of asphyxia occurred when the drugs were administered within three to four hours before delivery. From the point of view of analgesia and amnesia the heroin-hyoscine group proved to be the most effective.

WILLIAM BERMAN.

Howard, John P., Balovich, Vernon, Collins, Conrad G., and Adriani, John: Some Observations Upon the Effect of Certain Anesthetic Agents in Uterine Motility During Labor, Anesthesiology 10: 151, 1949.

A study of the effect of three methods of anesthesia on uterine motility was made during normal labor by means of a tocograph. Saddle anesthesia with Nupercaine (17 cases) had little effect on uterine tone, decreased the strength of uterine contractions, increased the interval between pains and decreased their duration, but had no effect on the rhythm. Ethylene anesthesia (18 cases) either increased or had no effect on uterine tone, decreased the strength of contractions, had no effect on the frequency of pains or the rhythm, and either had no effect or decreased the duration of pains. Cyclopropane anesthesia (7 cases) decreased the strength of uterine contractions; decreased or had no effect on the tone; and had no effect on rhythm, duration or frequency, except that in two of the seven cases it stopped contractions completely.

HARVEY B. MATTHEWS.

Mammary Glands

Rozansky, R., and Brzezinsky, A.: The Excretion of Penicillin in Human Milk, J. Lab. & Clin. Med. 34: 497, 1949.

The concentration of penicillin in human milk after intramuscular injection was studied in a series of thirteen women by a colorimetric modification of the serial dilution method of Kolmer in this careful study. Significant quantities were found in all but one case, within one hour after injection, gradually rising in level to four hours with a gradual fall thereafter. This rise was slower but more prolonged than the serum levels attained, for at the end of two hours the concentration of penicillin in the milk was 10 to 15 per cent of that in the serum while subsequently the milk level remained constant or rose, as the blood level fell.

The authors state that the penicillin sensitivity of most susceptible strains of bacteria encountered in Jerusalem lie within the range of levels demonstrated in human milk.

S. B. GUSBERG.

Cancer, Malignancies

Fasanotti, Armando: On So-Called Grape-Like Sarcoma of the Vagina in Infancy, Arch. obstet. e ginec. 53: 85-103, 1948.

The author, after reviewing two cases of so-called grapelike sarcoma of the vagina, concludes that a more appropriate term would be dysontogenetic tumor of the malignant rhabdomyoma type. He bases his classification on the age of the subject in whom these tumors are found, on embryological studies, and on the histological features which resemble those of tumors of the striated-muscle type, exactly as one sees in malignant rhabdomyoma. This histological interpretation, according to the author, is compatible with the gross

features of malignant rhabdomyoma that are found in hollow organs having a muscular layer. He compares the gross similarities, for example, of rhabdomyoma of the esophagus and bladder to the so-called grapelike sarcoma of the cervix and vagina.

Dr. Fasanotti then gives an excellent review of the literature with a thorough bibliography appended. The presence of striated muscle fibers has been reported by several authors, while others maintain that the finding of muscular elements is a constant histological feature. Several interesting theories are offered regarding the origin of the tumors.

FRANK A. GRACEFFO.

Russo, P. E., and Kelso, J. W.: Dysgerminoma, Radiology 52: 367, 1949.

The authors report a case of dysgerminoma with pulmonary metastases in a woman 48 years old with ten living healthy children, which is an interesting finding in view of the fact that this tumor is often associated with sexual underdevelopment or pseudohermaphroditism. Involvement of one or both ovaries with the neoplasm well encapsulated carries a good prognosis. The metastases to distant organs warrant a grave prognosis. The patient reported here survived for seven years. This patient was given male sex hormone and x-ray irradiation. Good palliation was obtained with administration of the male sex hormone in the beginning after which time it became much less beneficial.

WILLIAM BERMAN.

Cave, W. H.: Cancer of the Cervix as Seen in a Rural Community, South. Surgeon 15: May, 1949.

Approximately 17,000 women die annually of carcinoma of the cervix. Cancer of the uterus accounts for 30 per cent of all cancer appearing in women. The author reviews his experience with 71 cases of carcinoma of the cervix treated in a small community.

In the author's series the age of the patients varied from 17 to 93 years. Heredity apparently played no prominent part in the cause of cancer in this group, but parity was a definite predisposing factor. Most cases are seen late in the illness and therefore tests emphasizing the early diagnosis of carcinoma are more of academic than of practical interest to the investigator. Even the biopsies were taken simply for confirmation, the diagnosis being obvious from clinical examination. Fifty-one of the patients were treated with x-ray and radium with a mortality rate of 37.2 per cent at the end of two years from the first visit. Twenty patients were treated with surgery alone or combined x-ray and surgery with a mortality of 55 per cent.

The average duration of symptoms for the entire group prior to consultation with a physician was 12.6 months. Approximately 14 per cent of the patients were seen by a physician because of symptoms referable to the uterus within 3 months of the time diagnosis was made.

WILLIAM BICKERS.

Sayre, George P.: Cylindroma of the Vulva: Adenocarcinoma, Cylindroma Type, of the Vulva. Report of a Case of Twenty-Seven Years' Duration, Proc. Staff Meet., Mayo Clin. 24: 224, 1949.

In the case reported the patient was 32 years of age when she was first seen at the Mayo Clinic in September, 1924; at that time a small growth had been present in the region of the left Bartholin gland for four years. The tumor was excised, but complete removal was considered inadvisable because it had extended backward to involve the anal sphincter; postoperative radium therapy was employed. In 1931 a recurrent tumor was excised and three courses of lead phosphate therapy were given. In 1934 to 1936, repeated courses of radium therapy were given for recurrent small nodules; biopsy showed adenocarcinoma. There was rarefaction in the right femoral head, which may have been due to metastasis or to radium necrosis. When the patient was next seen in October, 1943, there was massive extension of the growth to the whole perineum and right buttock, with sloughing; radium therapy was again given after urethral dilatation. Roentgenological

examination in 1944 showed a metastatic nodule in the lung, which was treated with radium. The patient's general health remained good until 1946, when roentgenograms showed rarefaction of the left pubic bone and right femoral head; and later multiple nodules in the lungs. The patient gradually failed and died in January, 1947, twenty-three years after her first admission to the clinic and twenty-seven years after the first nodule had been noted.

The final microscopic examination of the tumor showed irregular cylinders of cells with central lumina, and marked connective-tissue overgrowth, in the primary tumor and the metastatic growths; extension of the tumor was by the perineural lymphatics. All these findings are characteristic of the cylindroma type of adenocarcinoma. The long and relatively benign course of the disease are also characteristic of this type of adenocarcinoma.

HARVEY B. MATTHEWS.

Complications of Pregnancy

Dodd, Harold: Operation for Severe Varicose Veins During Pregnancy, *The Lancet*, p. 606, April 9, 1949.

The author reviews previous papers dealing with the management of varicose veins aggravated by the pregnant state. He reports seventeen cases of severe varicose veins of the legs operated upon between the second and seventh month of gestation. Women incapacitated by venous engorgement are rehabilitated, and the incomplete benefits and dangers of injection therapy are avoided.

IRVING L. FRANK.

Maranon, G.: Diabetes Insipidus and Uterine Atony, *Brit. M. J.*, p. 769, Nov. 15, 1947.

The author records the history of a 17-year-old girl with this affliction during the subsequent twenty-six years. She married at the age of 28 years and despite scanty menses and some periods of amenorrhea conception occurred on four occasions. Three pregnancies went to term while the fourth terminated in a spontaneous abortion. Labor in all three instances was unsatisfactory and the only living infant was born following the repeated injection of pituitary substance. No mention is made of hemorrhage or the condition of the uterus following the termination of pregnancy. Repeated diagnostic tests failed to reveal the presence of an intracranial lesion that might possibly account for disease. Reference is made to cases reported by Cushing, Richet, and the author, where a lesion existed that destroyed the posterior lobe of the pituitary gland and repeated uterine atony developed.

R. GORDON DOUGLAS.

Menstruation, Dysmenorrhea, etc.

Rawlings, W. J.: Magnesium in Dysmenorrhea, *M. J. Australia* 1: 61, Jan. 15, 1949.

The author used 20 grains of magnesium gluconate daily beginning four to seven days before the expected period and continued it for two to four days after the period started. There were 15 cases of premenstrual dysmenorrhea, 13 of which obtained relief. There were 18 cases of menstrual discomfort, 14 of which got relief. The author's general routine is as follows: for premenstrual distress treatment commences seven days before the onset of the period and is continued up to and including the first day. For menstrual distress the treatment is given for four days before and for three days after the period starts.

WILLIAM BERMAN.

Newborn

Martyn, G.: Staphylococci in the Newborn, *Brit. M. J.*, p. 710, April 23, 1949.

This investigation was undertaken to determine the incidence of this organism in the nasopharynx and feces of 130 full-term, breast-fed infants cared for in nurseries of twelve bassinets during the first seven days of life. Resistance of such strains as were isolated

was determined with respect to penicillin and streptomycin. The author uses the term *Staphylococcus pyogenes* to indicate coagulase-positive strains with aureus colonies, while coagulase-negative strains with white colonies were designated *Staph. saprophyticus*.

Considering both sources, 100 per cent of the infants showed positive cultures, three-fourths of which were *Staph. pyogenes*. This organism was isolated from one-half the cultures from feces and in 62 per cent from the nasopharynx. The former result is greatly in excess of the reported incidence in the literature, which is explained by the selective nature of the technique employed. Over one-half of the strains recovered from both sources were penicillin resistant and all of these organisms produced penicillinase. Only four strains in all were resistant to streptomycin. In instances where special tests were carried out, there was a homogeneity in the staphylococcal flora of the nasopharynx and bowel as far as concerned susceptibility to penicillin and streptomycin in three-fourths of the cases.

The incidence of penicillin-resistant strains in this study was similar to that reported by other writers where the organisms were recovered from infections.

R. GORDON DOUGLAS.

Sorsby, Arnold: Penicillin Therapy in Ophthalmia Neonatorum, Brit. M. J. 2: 322, Aug. 30, 1947.

Dr. Sorsby studied the results of treating various types of infections in the eyes of 232 infants from May, 1945, to March, 1947. The instillation of a drop of aqueous solution (10,000 units per cubic centimeter) every minute for one-half hour and subsequently less frequent applications gave superior results to five-minute instillations of a solution with 2,500 to 10,000 units per cubic centimeter.

The employment of lamellae (400 to 1,000 units of commercial penicillin), an ointment 800 to 25,000 units per gram, an oily suspension (10,000 units per cubic centimeter) and 2 per cent methyl cellulose, 10,000 units per cubic centimeter, all gave uniformly poor results. In another series no local treatment whatsoever was used and 200,000 units of penicillin were injected intramuscularly for 4 doses at three-hour intervals. In all cases prior to commencement of treatment, smears, cultures, and scrapings of the palpebral conjunctiva were carried out. No failures occurred when an aqueous solution (10,000 units per cubic centimeter) was instilled according to the one-minute schedule or when the systemic system of treatment was used in infections caused by the gonococcus or *Staphylococcus aureus*. When the disease was caused by diphtheroids or a virus (as indicated by the presence of inclusion bodies) the poorest results were obtained.

It is significant to note that a total failure to respond to penicillin was not observed and in no case did penicillin treatment fail to influence the condition sufficiently to remove all anxiety within a matter of hours or even less. The exudate usually disappeared during the first thirty minutes when instillations were employed every five minutes. Tables with details of time factors, causative organisms, scheme of treatment, and results are given.

R. GORDON DOUGLAS.

Gordon, R. R.: Water-Soluble Vitamin K in the Newborn, The Lancet, p. 692, April 23, 1949.

Administration of a water-soluble vitamin K analogue to a series of fifteen newborn infants adequately prevented the lengthening of prothrombin time ordinarily apparent on the fourth day of life (and spontaneously reversible in a week), which was demonstrated in a control series of seventeen infants. The control group further illustrated that greatly prolonged prothrombin time is not necessarily followed by hemorrhagic manifestations. None of the fifty-two infants who received this watery preparation developed gluteal abscesses, which are a troublesome sequel of oily vitamin K injections.

IRVING L. FRANK.

Correspondence

The Rat Ovulation Test

To the Editor:

I recently had the opportunity to work with Dr. E. J. Farris at the Wistar Institute where I was able to observe the rat ovulation test performed many times. I was impressed by its simplicity, validity, and excellent clinical results. It was therefore with great concern and assiduousness that I read the article by Levin, Buxton, and Engle (*AM. J. OBST. & GYNEC.* 58: 795-798, 1949) who attempt to disprove the test.

After a careful perusal of their publication one notes the following salient features. The technique advocated by Farris in previous communications is not adhered to in that the strain of the rats used is not stated and fluorescent lamps were substituted for the special lamp suggested. Both of these requisites contribute immeasurably to the success of the test. Nevertheless, in two of the three cases in which laparotomy was performed (Cases of A. B. and A. S.) ovulation occurred or was absent as predicted in the criteria for reading the hyperemia response. In the third instance, the Case of B. P. where evidence of ovulation was found on laparotomy, incomplete testing is to be found. No urine collections were made on important cycle days thirteen and fifteen.

In the other four cases discussed by the authors one cannot argue with positive proof in either direction in view of the lack of true objective evidence.

It must therefore be re-emphasized that the ability to interpret adequately these hyperemic responses in rat ovaries and to follow the prescribed techniques is of prime importance before true comparative studies may be evaluated.

ALVIN M. SIEGLER, M.D.

706 EASTERN PARKWAY,
BROOKLYN, N. Y.
NOVEMBER 14, 1949.

Response by Drs. Levin, Buxton, and Engle

To the Editor:

Dr. Siegler infers that our¹ inability to confirm the optimistic claims of Farris may be due to several factors. His first objection concerns the strain of animals we used. These were rats of the Long-Evans strain derived from a colony inbred in this laboratory for more than twenty years. The exact ages of the rats are known and only those 21 to 24 days old were used. There is a remote possibility that animals of this strain are less responsive than are those of other strains to gonadotrophin (if this is indeed the principle responsible for the positive "ovulatory" reaction). However, this factor does not appear to enter into the discrepancy for, as stated in our paper, at least one "positive" control rat was included in each day's test. The "positive" control was injected with urine from women known to be in the first trimester of pregnancy. Every one of these "positive" controls, without exception, showed a definite hyperemic reaction of the ovaries. This proved, at least to our own satisfaction, that the animals do unquestionably respond when adequately treated with gonadotrophin.

The results obtained with the "positive" controls also appear to vitiate Dr. Siegler's objection relating to the type of light used. It is true that we examined the test animals' ovaries under a battery of fluorescent lights instead of the special lamp used by Farris. Nevertheless, when animals showed a positive response, as did those injected with pregnancy urine, we had no difficulty in recognizing such a response. It seems reasonable to assume that we could as readily recognize a positive response caused by urine from an ovulatory woman.

Dr. Siegler also attempts to make the point that our results are better than we claim. He suggests that the ovulation of subject A. B. was in actuality predicted by the hyperemia reaction while in subject B. P. the lack of tests on days 13 and 15 makes interpretation impossible. Dr. Siegler's point is correct only if there has been a further revision of Farris' criteria of a "positive" ovulatory response. Originally² it was stated that a positive hyperemia response for at least three successive days is required to demonstrate a "normal" ovulation. Later, apparently on the basis of additional experience, Farris³ stated that *four successive days of positive hyperemia* are required to indicate a "normal" ovulatory pattern. In line with this latest requirement, neither subject A. B. nor B. P. showed a normal ovulatory pattern. Subject A. B. showed three days of doubtful positive reaction followed by one day of full positive reaction. A normal ovulation could not be diagnosed for B. P. even if positive responses had been obtained on days 13 and 15, for even in this event there would have been only two successive days of positive response, two days less than Farris' latest requirement. The response obtained from A. S. cannot be debated. It is true that a positive response was not obtained nor was any indication of ovulation found at laparotomy.

The other four of our subjects were gynecologically normal. Although laparotomy was not done to examine the ovaries of these subjects, the basal body temperature curves showed the changes which many investigators now accept as indicative of ovulation. As suggested in our report, we also consider "the only certain means of proof is by appropriately timed laparotomy with subsequent microscopic examination of the ovaries." By the same token (and this we attempted to indicate in our original paper) Farris has not yet proved his point. Therefore his test still "must remain as an interesting but unproved suggestion."

LOUIS LEVIN, PH.D.
C. L. BUXTON, M.D.
E. T. ENGLE, PH.D.

NEW YORK.
NOVEMBER 30, 1949.

References

1. Levin, L., Buxton, C. L., and Engle, E. T.: AM. J. OBST. & GYNEC. 58: 795, 1949.
2. Farris, E. J.: AM. J. OBST. & GYNEC. 52: 14, 1946.
3. Murphy, D. P., and Farris, E. J.: AM. J. OBST. & GYNEC. 54: 467, 1947.

Reply by Dr. Farris

To the Editor:

In the October, 1949, issue of this JOURNAL, an article by Louis Levin, C. L. Buxton, and Earl Engle appeared, which questioned the value of the hyperemia method for the determination of ovulation time.

The technique recommended by me for ovulation timing was said by Levin, Buxton, and Engle to have been followed by them. In my early experiments, after consultation with General Electric Co. lighting engineers, it was decided that the specially selected fluorescent lights chosen for daylight color were unsatisfactory for reading hyperemia in the rats' ovaries. In our work, we use the Macbeth light No. ADP 20. This has proved to be quite satisfactory for reading of different shades of the same color. Since Levin and associates used fluorescent lights, and not a Macbeth light, their technique differed in this respect from mine.

The essayists did not state whether they used the Wistar strain of rats. In our early testing we learned that other strains are usually less sensitive than the Wistar rat for this type of testing. This has been confirmed several times by other workers who were furnished our rats for testing of ovulation time, when the other strains employed failed to give consistent reactions.

It has been shown, further, that illuminating gas must be employed, and the rats killed individually. Chloroform and ether do not give the same color reactions, and are unsatisfactory for ovulation testing. It is therefore obvious that the methods recommended must be followed.

Let us consider in detail only the three instances in which laparotomies were performed. Such objective evidence is more valuable than that obtained from the other four cases, in which the findings were interpreted by the authors.

In the case of A. B., aged 39 years, the test is definitely confirmatory. Hyperemia for four consecutive days on cycle days 11 through 14, followed by a negative or no reaction, is typical of the normal ovulation reaction (Farris¹). By my interpretation, it is likely that ovulation occurred late on the 14th cycle day, and microscopic examination of the ovary would in all likelihood have revealed luteal tissue of about 72 to 96 hours in age. The authors, upon laparotomy, found a ruptured hemorrhagic cyst. Our experience indicates that a bleeding corpus luteum cannot be read accurately by gross examination, for bleeding and oozing may last for as long as approximately three days after ovulation (Farris, Lewis, Bachman, and Muckle²). In this case, their findings confirmed the validity of the test.

In the case of B. P., aged 39 years, the patient failed to collect urines for two days at the critical period during the growth of the follicle, or on cycle days 13 and 15. Such a test is incomplete, and as a rule interpretations should not be attempted. However, if interpretation were insisted upon, one could assume that if cycle days 13 and 15 were positive, together with the only strong positive reaction indicated on cycle day 16, it is likely that ovulation took place late on cycle day 16. Surgery on cycle day 17 should have revealed a corpus hemorrhagicum. Likewise, this split reaction is abnormal in character, and if coitus were attempted, conception would not be achieved. It must be emphasized that such incomplete testing at critical days in the zone of ovulation is practically useless. The weak responses on cycle days 18 and 20 are not uncommon, and do not affect the interpretation.

In the case of A. S., aged 27 years, a hyperemia was lacking on cycle days 11 to 15, the only days in the entire cycle that were tested. My interpretation of this negative reaction is that it is indicative of "no ovulation" at this period, and in accordance with the essayists' findings, as evidenced by laparotomy.

The essayists stated, "The surgical procedures were timed to occur on the day after ovulation, as judged by the sudden rise in basal body temperature." It is incomprehensible that the authors could employ the temperature patterns exhibited in two of these cases to select the time of ovulation, as indicated by the so-called "sudden rise." Examination of the temperature records reveals that there is no obvious sudden rise in two of the three cases. I would agree with a previous statement of one of the authors (Buxton³), who reported on 127 temperature records. He stated that three-fourth of these were atypical. He concluded that it is practically impossible to predict the time of ovulation from knowledge of the temperature curve.

If the temperature records of these three patients represent the ease with which the authors can establish ovulation time, this method should be much more effective in aiding subfertile women to conceive. However, the facts relative to temperature compared with the rat test for prediction of human ovulation are available in one of my previous papers (Farris⁴).

It has been my privilege to examine human ovaries obtained from three different hospitals and from a group of 150 women subjected to operation in whom the time of ovulation was determined by the method described by Farris.¹ The ovaries were obtained at surgery (Farris and others²) at specified times (a) during growth of the follicle and (b) at representative intervals after ovulation.

Several of these ovarian specimens were submitted to Dr. G. W. Corner for his estimate as to the age of the particular corpus luteum. This he ascertained microscopically, basing his findings upon his experience in determining the age of the corpus luteum in the rhesus monkey by histological examination. Dr. Corner, Jr., later examined the speci-

mens of endometrium of these patients, and also independently judged the time of ovulation. In the majority of specimens examined, there was agreement between the predicted age based on the rat test, and the age estimated by microscopic examination of both the endometrium and the corpora lutea. A paper⁵ based on this work is in press, and will appear in this JOURNAL.

It is unnecessary to discuss in detail the other four cases. The essayists admit that one case in the four showed a normal reaction. If their technique in the conduct of the test had been according to the standards, I would agree that the other three cases showed abnormal reactions.

In a series of sterile couples in which the husbands are fertile, it has been found by me that at least 50 per cent of the ovulation reactions of the wives were abnormal. These women had been classified by gynecologists as clinically normal in all respects and they should have conceived. However, these women failed to conceive during the months in which their ovulation reactions appeared abnormal. It is likely that abnormal ovulations are one of the chief causes of reduced fertility.

Quoting from the summary and conclusions of my first paper on this subject (Farris¹), item 5, "Results thus far indicate the third or fourth day of a normal reaction as the time when insemination is most likely to produce pregnancy." Examination of our findings to date indicates that 48 per cent of the pregnancies have occurred, following a single artificial insemination, in ovulation cycles of four days in length. The ranges for the normal reactions vary from three to six days. These ranges are based upon several thousand tests, and at least 150 conceptions which were achieved through the aid of our laboratory.

It should be called to attention that the author¹ attempted in the first paper to show a trend in ovulation. The legend for Table III carried the notation, "Note that the reactions occur earlier in the shorter cycles than in the longer cycles. Patients with normal reactions became pregnant when coitus was planned in relation to the ovulation reaction." The records showed admittedly incomplete testing in some of these cases, and consequently these may have been confusing. The table was intended primarily to show trend only. However, in Table IV, in which the abnormal reactions were listed, it should be noted that individuals showed interrupted or split color reactions, as reported.

Conceptions occurred in cycles where ovulation was predicted, in each instance, and when isolated coitus or artificial insemination was attempted. In many of the cycles, before conception occurred, ovulation testing gave stated abnormal reactions, and the causes for anticipated failure were predicted and stated (Murphy and Farris⁶).

Gonadotrophic assays done by Dr. A. E. Rakoff are commented upon as being too high. Rakoff and others consider 16 to 32 rat units to be within normal range.

It appears that the difficulties encountered by Levin, Buxton, and Engle are, briefly, two: (1) The inability to interpret their findings properly, and (2) failure to follow precisely the technique as recommended.

We have had numerous visitors in our laboratory who have learned our procedures, and many are reporting successful results. Our laboratory is open to the essayists and others, to view the proper technique, learn our interpretations, and put the test to practical use, if they so desire.

EDMOND J. FARRIS.

PHILADELPHIA, PA.
DECEMBER 2, 1949.

References

1. Farris, Edmond J.: *AM. J. OBST. & GYNEC.* 52: 14, 1946.
2. Farris, Edmond J., Lewis, Warren H., Bachman, Carl, and Muckle, Craig W.: *Anat. Rec.* 100: 766, 1948.
3. Buxton, C. L.: The Atypical Secretory Phase, read at the Conference on Menstruation and Its Disorders, National Committee on Maternal Health, New York, 1947.
4. Farris, Edmond J.: *J. A. M. A.* 138: 560, 1948.
5. Corner, George W., Farris, Edmond J., and Corner, George W., Jr.: *AM. J. OBST. & GYNEC.* (In press.)
6. Murphy, Douglas P., and Farris, Edmond J.: *J. A. M. A.* 138: 13, 1948.

Items

Residency Training Requirements

The American Board of Obstetrics and Gynecology has not made nor is it contemplating any changes in its residency training requirements, despite rumors of an increase in training years. Eligibility requirements remain the same, namely, three years of acceptable formal training, followed by at least two years of posttraining practice in the specialty.

Hospitals are inspected and approved for training jointly by the Council on Medical Education and Hospitals of the American Medical Association and this Board. Approvals are granted for training periods of one, two, and three years depending on the available facilities and the findings of the survey inspections.

This Board has no objection to residency services being arranged by hospitals for periods longer than three years, unless this dilutes the candidate's clinical training opportunities too much during the first three years. However, the Board does not accept a fourth year, or more, of residency training as a substitute for any part of the required two years of posttraining practice.

The importance of posttraining practice in the specialty is emphasized as an opportunity for maturing of the candidate and for colleague appraisal of a man's ability when working on his own responsibility in his chosen community. The only exception to this ruling is in the case of men advancing from their training into full-time teaching positions. These men then must complete at least two years in such positions.

Copies of the Bulletin of this Board, outlining the above requirements in more detail, are available to hospital administrators or to candidates, upon application.

PAUL TITUS, M.D., Secretary,
American Board of Obstetrics and Gynecology,
1015 Highland Building,
Pittsburgh 6, Pa.

Diplomate

The following physician is to be included in the list of diplomates of this Board: Maurice J. Meynier, Jr., M.D., 1601 Calhoun St., Houston, Texas.

PAUL TITUS, M.D., Secretary,
American Board of Obstetrics and Gynecology,
1015 Highland Building,
Pittsburgh 6, Pa.

Sterility Award

The American Society for the Study of Sterility is offering an Annual Award of \$1,000 known as the Ortho Award for an essay on the result of some clinical or laboratory research pertinent to the field of sterility. Competition is open to those who are in clinical practice as well as to individuals whose work is restricted to research in basic fields or full-time teaching positions. The Prize Essay will appear on the program of the forthcoming meeting of the American Society for the Study of Sterility, which is to be held at the Sir Francis Drake Hotel in San Francisco on June 24 and 25, 1950.

Full particulars may be obtained from the Secretary, Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield 8, Mass. Essays must be in his hands by April 1, 1950.

Notice of Annual Meeting

June 24-25, 1950. The American Society for the Study of Sterility, Sir Francis Drake Hotel, San Francisco, Calif. Secretary-Treasurer, Walter W. Williams, M.D., 20 Magnolia Terrace, Springfield 8, Mass.